CASE AUTH/2146/7/08

PRIMARY CARE TRUST CHIEF PHARMACIST v SANOFI-AVENTIS

Plavix leavepiece and conduct of a representative

The chief pharmacist at a primary care trust complained about the promotion of Plavix (clopidogrel) by Sanofi-Aventis and about the conduct of its representative. Materials at issue were a leavepiece and a reply paid card.

The complainant was very concerned that the representative had left the leavepiece with a GP practice and in a meeting had verbally linked The Reduction of Atherothrombosis for Continued Health (REACH) registry study with a lifelong need for Plavix. The complainant submitted that the output from the REACH registry gave no grounds for choosing one antiplatelet over another.

The complainant rather suspected that the detail aid should have been withdrawn from use as she had received a later version via the co-marketer, Bristol-Myers Squibb. This did not refer to Plavix whereas the earlier version contained the SPC despite not naming the product in the body of the text. However, the complainant did not feel that it was an innocent mistake in view of the conversations.

The complainant considered that it was an example of misleading and unwarranted promotion.

The detailed response from Sanofi-Aventis is given below.

The Panel noted that the REACH registry sought to compile an international data set to extend knowledge of atherothrombotic risk factors and ischaemic events in the outpatient setting. The registry, supported by Sanofi-Aventis and Bristol-Myers Squibb, provided an opportunity to measure both ischaemic events rates and use of risk reduction therapies in a large population.

The Panel examined the detail aid used by the representative. The front page described the protection offered by Plavix compared with aspirin. The next two pages (double page spread) described the REACH registry and data relating to the risk of cardiovascular death, myocardial infarction (MI), stroke or hospitalisation for other atherothrombotic events within the first year. The next double page spread set out details of a patient and asked how that patient should be treated followed by information from CAPRIE which showed a relative risk reduction of 23% in the subgroup of patients who had peripheral arterial disease or stroke and previous MI. The detail aid stated that these benefits were maintained for up to 3 years and that 26% of patients in CAPRIE fitted the REACH registry profile, with vascular disease in more than one location. A red line ran across the bottom of all of the pages of the detail aid seemingly linking them together. One each right hand page and on the front and back pages, the line incorporated the Plavix product logo. In that regard the Panel considered that the double page spread detailing the REACH registry could be seen as linking that study to the use of Plavix.

The Panel noted that in his presentation the representative had introduced himself and stated that he wanted to talk about Plavix in atherothrombosis. The representative then referred to the REACH registry using the detail aid which featured the Plavix product logo, he then described the CAPRIE trial and concluded the presentation by referring back to the REACH registry data in the detail aid, confirming that patients with vascular disease in two or three locations would be ideal targets for Plavix. Each attendee was given a REACH leavepiece which included the prescribing information for Plavix.

The Panel noted that the representatives' briefing document stated under key messages that 'REACH supports the use of Plavix within the current strategy in the management of the multi-vascular patient with established atherothrombosis'. In the Panel's view this was misleading as it directly associated the REACH registry with Plavix. The REACH registry established the need for treatment in general whilst the CAPRIE study supported the use of Plavix in particular. The briefing document mixed up these two messages and thus advocated a course of action which was likely to lead to a breach of the Code. A breach of the Code was ruled.

The Panel considered that it was impossible to know exactly what had been said at the meeting. Nonetheless, bearing in mind the briefing material and given the structure and content of the Plavix detail aid and of the representative's presentation, the Panel considered that on the balance of probabilities, attendees at the meeting would be left with the impression that the REACH registry supported the use of Plavix *per se*. This impression would be strengthened by the use of the REACH leavepiece which incorporated the prescribing information for Plavix. The Panel considered that it was misleading to link the REACH registry data to the use of Plavix in particular. A breach of the Code was ruled.

The Panel considered that the representative had,

by following the briefing material and using the detail aid and leavepiece, structured his presentation such that a misleading impression had been given with regard to the REACH registry and Plavix. Although the representative had used material provided by the company and followed company instructions all the relevant requirements of the Code had not been complied with. Thus a further breach was ruled.

The chief pharmacist at a primary care trust complained about the promotion of Plavix (clopidogrel) by Sanofi-Aventis and about the conduct of its representative. Materials at issue were a leavepiece and a reply paid card (both referenced PLA07/1081).

Plavix was an antiplatelet medicine indicated for the prevention of atherothrombotic events in patients suffering from myocardial infarction (MI) (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease. It was also indicated for patients suffering from acute coronary syndrome in line with the conditions set out in the summary of product characteristics (SPC).

COMPLAINT

The complainant was very concerned that a Sanofi-Aventis representative had left the leavepiece with a GP practice. He also verbally linked The Reduction of Atherothrombosis for Continued Health (REACH) registry study with a lifelong need for Plavix. The complainant had confirmed that this was the impression given by the representative at a practice meeting with all five doctors. The output from the REACH registry gave no grounds for choosing one antiplatelet over another.

The complainant rather suspected that the detail aid should have been withdrawn from use as she had received a later version via the co-marketer, Bristol-Myers Squibb. This did not refer to Plavix whereas the earlier version contained the SPC despite not naming the product in the body of the text. However, the complainant did not feel that it was an innocent mistake in view of the conversations.

The complainant considered that it was an example of misleading and unwarranted promotion.

When writing to Sanofi-Aventis, the Authority asked it to respond in relation to Clauses 7.2, 15.2 and 15.9 of the 2008 Code which were the same as the 2006 Code.

RESPONSE

Sanofi-Aventis submitted that the REACH registry was an epidemiological study that explored the risk of events and management of patients with atherothrombosis. The registry was independently run and sponsorship was provided by Sanofi-Aventis and Bristol-Myers Squibb. Baseline prevalence data were published in JAMA in 2006 and one-year follow-up data in early 2007 (also in JAMA). This registry was of major importance as it was the largest and most current assessment of the burden of atherothrombotic disease. It was not designed to investigate the effectiveness of any individual therapeutic agent and no such data had been reported from the registry.

The representative had been a pharmaceutical sales representative for many years including ten years with Sanofi-Aventis. He was trained on the Code at his initial training course with Sanofi-Aventis and via the company 'I-Learn' training system, to which he had continuous access as a reference tool. He had passed his ABPI examination and it was understood that there had been no previous history connected with his conduct against the Code, either in Sanofi-Aventis or with his previous employer.

The representative had been trained on Plavix in two days of on-line coursework with an on-line assessment, three days of classroom tuition with a written assessment and a series of practical role play assessments taking into account a variety of scenarios and customer groups. He completed his training successfully. In addition, he attended a two day refresher course at which he received additional training around clinical data relating to Plavix. He had successfully passed the course assessments.

The representative attended the practice to provide lunch and deliver a presentation, prior to its internal weekly meeting. According to the representative, the meeting was attended by five GPs, two nurses, the practice pharmacist, the practice manager and his assistant. The representative started his presentation at about 1.05pm and, after introducing himself, he explained that he wanted to talk about Plavix and its use in atherothrombosis using the Plavix primary care detail aid (PLA07/1601) to support his talk. From his recollection, the group was positive towards Plavix and one doctor explained his satisfaction towards its lack of side effects. The doctor also confirmed that the hospital requested that patients stayed on Plavix for 12 months before being discharged. The representative continued the discussion by highlighting the two indications for Plavix: acute coronary syndrome for which 12 month treatment was appropriate and atherothrombosis which was what he wanted to discuss.

The representative then introduced the REACH registry data from the sales aid. From recollection he explained that from the data, those patients with disease in one vascular location, had a 1 in 10 likelihood of a further event or hospitalisation within the next 12 months. This, however, increased to a 1 in 5 chance when a patient had disease in two locations. He confirmed that patients within the REACH registry were on conventional therapy including ACE inhibitors, beta blockers, statins and

aspirin, and despite this, these patients went on to have further events or were hospitalised in the next 12 months.

The representative then introduced the CAPRIE trial, a comparison of Plavix and aspirin in 19,185 patients. From recollection, he explained that the outcome of the study was that there was a 9% relative risk reduction in favour of Plavix over aspirin in preventing further MI, stroke or vascular death. He recalled that the group felt that these were reasonable results but was concerned about the cost of Plavix compared with aspirin in a large group of patients.

The representative then explained that in a subgroup analysis of the CAPRIE trial looking at patients with peripheral arterial disease or stroke and previous MI that the relative risk reduction was significantly greater than in the overall trial. This information received a positive response from those at the meeting.

He concluded the presentation by referring back to the REACH registry data in the sales aid, confirming that patients with vascular disease in two or three locations would be ideal targets for the use of Plavix, which the group confirmed it would consider. He then thanked the group for attending and gave each doctor a copy of the REACH leavepiece (PLA07/1081), which included prescribing information for Plavix. The representative left the surgery at about 1.15pm.

Overall, the account of the presentation given by the representative was very much in line with his previously observed customer interactions. His usual style of customer communication contained a high level of information delivery, in the structure set out within the sales aid with a consistent approach of maintaining the discussion in line with the marketing brief.

All sales representatives who promoted Plavix were comprehensively trained and briefed on the product and therapy area.

As stated previously the REACH registry was an epidemiological study that explored the risk of events and use of several therapies in patients with atherothrombosis. It did not, as the complainant rightly stated, give grounds for one antiplatelet to be used over another as it neither captured the use of specific agents nor was designed to explore therapeutic effect. This had been communicated clearly and consistently in the material used by the representatives and in the training they had received. This was supported by the information contained in the leavepiece and memorandum and in all subsequent briefing material: training material (PLA07/1502), section 8-9; key message brief (PLA07/1245), May 07; key message brief (CV07/1177), Nov 07; resource guide (PLA07/1578), Dec 07 and brand book (CV08/1041), May 08.

The basis for the promotion of the efficacy of Plavix in patients with atherothrombosis was the CAPRIE study, as explicitly included in all the above materials. Throughout these materials, REACH was used as the substantiation for statements on the burden of disease and it was never used to back up claims or statements regarding Plavix. The briefing document on the publication of REACH 1-year results commented that 'REACH supports the use of Plavix…' immediately prior to presenting the registry results and then followed this, separately, by referring to Plavix efficacy in the CAPRIE study. The need to 'tie back' the results of the registry to 'how Plavix can help protect these patients' was specifically referred to in the concluding section – which would clearly be unnecessary if the registry was presented as having itself incorporated Plavix data or usage.

The leavepiece left by the representative and the supporting briefing memorandum (PLA07/1147) were reviewed, approved and certified in March 2007. The theme of this item was that the REACH registry provided evidence of the burden of disease and the increasing risk of atherothrombotic events in patients with atherothrombosis in relation to number of vascular beds affected. This item was no longer in use and had not been superseded.

The promotional aid used in the meeting was a Plavix primary care detail aid (PLA07/1601) and the content clearly distinguished between the burden of disease, as shown by REACH, and the effect of Plavix on patients with atherothrombosis, as shown by CAPRIE.

Sanofi-Aventis explained that the reason one leavepiece had prescribing information [referred to as 'the SPC' by the complainant] and one subsequently presented by Bristol-Myers Squibb (PLA07/1361) did not, was that they were developed for two very different audiences. The leavepiece left by the representative was for use with prescribers during detailed discussion on Plavix, to provide more detail on REACH and the burden of disease, and also to allow them to request additional information if so desired. When the leavepiece was developed, it was considered that prescribing information would be appropriate as it was to be used in a detailed Plavix sales call with prescribers. In this context, and given that prescribing information was by its nature, non-promotional and contained no product claims, this was a conservative view taken with the intention of providing appropriate information in keeping with the spirit of the Code. Sanofi-Aventis noted that the rest of the leavepiece did not refer to Plavix, nor was Plavix livery or typography used in this item.

The separate REACH item with no prescribing information was developed for use by Sanofi-Aventis/Bristol-Myers Squibb market access/healthcare teams for use with non-prescribers to stimulate a dialogue on the burden of disease at a population level and it was deemed that prescribing information was not necessary due to the different context in which this item was to be

used.

In summary, Sanofi-Aventis took great care to appropriately train and brief its representatives and develop materials which accurately reflected the content and implications of the REACH registry. Active consideration was given to the context and audience for each of the materials in question, with reference to both the letter and spirit of the Code. The detailed account of the meeting from the representative did not support the complainant's allegations that he misled his audience. Overall, Sanofi-Aventis believed that high standards had been maintained, both by the representative and the company in general, and the materials used in the relevant training, briefing and sales activities had been constructed to avoid misleading the recipient and/or customers. Any allegation of breaches of Clauses 7.2, 15.2 and 15.9 was refuted.

PANEL RULING

The Panel noted that the REACH registry sought to compile an international data set to extend knowledge of atherothrombotic risk factors and ischaemic events in the outpatient setting. Patients aged ≥45 years with at least 3 atherothrombotic risk factors or documented cerebrovascular coronary artery or peripheral arterial disease were to be involved. The REACH registry offered an opportunity to provide a better understanding of the prevalence and clinical consequences of atherothrombosis in the outpatient setting in a wide range of patients from different parts of the world. The REACH registry provided an opportunity to measure both ischaemic events rates and use of risk reduction therapies in a large population. Sanofi-Aventis and Bristol-Myers Squibb supported the registry.

The Panel examined the detail aid used by the representative (PLA07/1601). The front page described the protection offered by Plavix compared with aspirin. The next two pages (double page spread) described the REACH registry and data relating to the risk of cardiovascular death, MI, stroke or hospitalisation for other atherothrombotic events within the first year. The next double page spread set out details of a patient and asked how that patient should be treated followed by information from CAPRIE which showed a relative risk reduction of 23% in the subgroup of patients who had peripheral arterial disease or stroke and previous MI. The detail aid stated that these benefits were maintained for up to 3 years and that 26% of patients in CAPRIE fitted the REACH registry profile, with vascular disease in more than one location. A red line ran across the bottom of all of the pages of the detail aid seemingly linking them together. One each right hand page and on the front and back pages, the line incorporated the Plavix product logo. In that regard the Panel considered that the double page spread detailing the REACH registry could be seen as linking that study to the use of Plavix.

The Panel noted the structure of the presentation given by the representative. Sanofi-Aventis had submitted that the representative had introduced himself and stated that he wanted to talk about Plavix in atherothrombosis. The representative then referred to the REACH registry using the detail aid which featured the Plavix product logo, he then described the CAPRIE trial and concluded the presentation by referring back to the REACH registry data in the detail aid, confirming that patients with vascular disease in two or three locations would be ideal targets for Plavix. Each attendee was given a REACH leavepiece which included the prescribing information for Plavix.

The Panel noted that the representatives' briefing document (PLA-07/1147) stated under key messages that 'REACH supports the use of Plavix within the current strategy in the management of the multi-vascular patient with established atherothrombosis'. In the Panel's view this was misleading as it directly associated the REACH registry with Plavix. The REACH registry established the need for treatment in general whilst the CAPRIE study supported the use of Plavix in particular. The briefing document mixed up these two messages and thus advocated a course of action which was likely to lead to a breach of the Code. A breach of Clause 15.9 was ruled.

The Panel considered that it was impossible to know exactly what had been said at the meeting. It appeared that the complainant had not been present. Nonetheless, bearing in mind the briefing material and given the structure and content of the Plavix detail aid and of the representative's presentation, the Panel considered that on the balance of probabilities, attendees at the meeting would be left with the impression that the REACH registry supported the use of Plavix *per se*. This impression would be strengthened by the use of the REACH leavepiece which incorporated the prescribing information for Plavix. The Panel considered that it was misleading to link the REACH registry data to the use of Plavix in particular. A breach of Clause 7.2 was ruled.

The Panel considered that the representative had, by following the briefing material and using the detail aid and leavepiece, structured his presentation such that a misleading impression had been given with regard to the REACH registry and Plavix. Although the representative had used material provided by the company and followed company instructions all the relevant requirements of the Code had not been complied with. Thus a breach of Clause 15.2 was ruled.

Complaint received **23 July 2008**

Case completed **1 October 2008**