PHARMACIST PRACTITIONER v SANOFI-AVENTIS

Conduct of representative

A pharmacist practitioner at a general practice complained that, during the course of promoting Lantus (insulin glargine) and Acomplia (rimanobant), a representative from Sanofi-Aventis displayed an apparent lack of knowledge about the data.

The representative claimed that a flowchart from the American Diabetic Association (ADA) advised the use of basal insulins such as Lantus second line to metformin in type 2 diabetics. The complainant had since found this flowchart online; those present were not allowed a close look at this information at the meeting. While this was a recommendation, it was actually one of the three interventions advised. The same page as the flowchart stated 'Early initiation of insulin would be a safer approach for individuals presenting with weight loss, more severe symptoms, and glucose values >250-300 mg/dl'. This was not the impression given by the representative; it was intimated that basal insulins were being recommended in this advice as second line to metformin for all type 2 diabetics.

Of greater concern was the information given about Acomplia. Again the representative presented information that was not passed around or left to allow a closer look but the complainant was certain that the data came from the RIO-Diabetes study. However, the representative wrongly stated that the patients were newly diagnosed and treatment naïve when in fact all had been on oral therapy for 6 months in randomisation. Conversely, the SERENADE study was conducted in treatment naïve diabetics, however the trial was currently unpublished and the indication studied remained unlicensed. It seemed that the representative was confused about these separate studies and had presented data from the two as if they were one and the same.

The representative then stated that other practices were, based on these data, using Acomplia as a third line hypoglycaemic in diabetics, in place of glitazones. Acomplia was not licensed as a hypoglycaemic and he did not think it should be promoted on this basis.

Further comments were sought from the complainant on receipt of the company's response. The complainant was not questioning the use of ADA/ESAD guidelines in general but the way that they were presented. The flowchart clearly indicated three treatment alternatives and that only one of these was discussed, without making it clear there were three, misrepresented the data.

The complainant noted that Sanofi-Aventis had submitted that the data were presented in line with the current marketing authorization and not presented in relation to diabetes. Despite this assertion the detail aid made it very clear that the SERENADE study was conducted in overweight patients with type 2 diabetes who were inadequately controlled! Additionally, in discussion the representative specifically referred to patients with diabetes (following on from the discussion about Lantus) and diabetes medicines. The complainant considered that the detail aid implied that Acomplia could be used as an agent to reduce HbA_{1C}.

The complainant had left the meeting and returned to hear the representative talking about the use of Accomplia instead of glitazone. He therefore sought clarification of the representative's comments whereupon he was told that Acomplia could be used in place of hypoglycaemics and in fact this was being done in other practices locally. The clarification the complainant sought was based on his surprise that Acomplia was apparently touted as an alternative to hypoglycaemics. At no time did the representative mention that such use would be outside the marketing authorization nor did he state that Sanofi-Aventis could not support such use.

Finally, the complainant advised that three other health professionals (a diabetes practice nurse and two doctors) were also present at the meeting and all three had stated that the representative had left them with the impression that Acomplia could be used to reduce HbA_{1C} in type 2 diabetics.

The Panel noted that the guideline as shown in the Lantus detail aid clearly detailed three treatment options for patients who failed to reach an HbA_{1C} target of >7% namely; 'Add basal insulin - most effective'; 'Add sulphonylurea - least expensive'; or 'Add glitazone - no hypoglycaemia'. The Panel noted the representative's statement that 'At no point… did I state or imply that basal insulin was the only option available to them, I clearly stated that it was another option available'. The representatives' briefing material however recommended that representatives focused on the left hand side of the page (the basal insulin option) and led discussion around the positioning of basal insulin. Nonetheless there was no implication in the briefing material that basal insulin was the only option mentioned in the guideline; it was referred to as 'a treatment'. The Panel also noted that the representative also denied that he had intimated that basal insulins were recommended as second line treatment to metformin for all diabetics. The Panel considered that it was impossible in such circumstances to determine on the balance of probabilities exactly how the guideline had been presented. No breach of the Code was thus ruled.

The Panel noted each party's submission in relation to the Acomplia data. The representative stated that he had made it clear that he was discussing the SERENADE data and not the RIO-Diabetes study. The Acomplia detail aid clearly referred to the SERENADE study. It appeared that the complainant was concerned that he in error had referred to the RIO-Diabetes study but that this error had not been corrected by the representative. It was impossible to determine on the balance of probabilities what had been said and the Panel thus ruled no breach of the Code.

The Panel noted that Acomplia was licensed as an adjunct to diet and exercise for the treatment of obese patients (BMI>30kg/m^2) or overweight patients (BMI>27kg/m^2) with associated risk factors, such as type 2 diabetes or dyslipidaemia. The Panel noted that the detail aid referred to overweight patients. The relevant representatives' briefing material began 'Identify overweight patients with type 2 diabetes as the patient group we would like to discuss'. This was not unacceptable. Again the Panel considered that it was impossible to determine on the balance of probabilities exactly what had been said and ruled no breach of the Code.

The Panel noted that according to both parties the discussion of Acomplia had included mention of glitazones. Both parties also agreed that the complainant had asked a question about this matter. However the parties' accounts differed. In addition the complainant had been absent for the beginning of the relevant discussion and had returned during a discussion about the use of Acomplia instead of a glitazone and had sought clarification of the representative's comments. The complainant did not provide his understanding of how this discussion had started. According to Sanofi-Aventis in response to a question about Acomplia and diabetics the representative explained that local practices used Acomplia in type 2 diabetics in whom weight loss was appropriate. Thereafter, when asked if it was being used in place of other medicines the representative stated that some local practices had used Acomplia in place of a glitazone. The Panel did not accept the company's suggestion that it could rely on the exemption to the definition of promotion set out in the Code. If the company's version of the discussion was correct it did not appear that the representative had necessarily been asked about replacement of glitazone with Acomplia.

The Panel noted that representatives could respond to unsolicited questions about the unlicensed use of their products so long as the criteria set out in the supplementary information were satisfied. Representatives should be extremely cautious when responding to such requests. It was difficult for representatives to satisfy the criterion given their role, particularly at a group promotional meeting. Attendees were likely to view the representatives' comments in the context of promotion. The safest course of action was to forward such requests to the company's medical information department.

Whilst there were some similarities the parties' accounts differed. In particular the complainant was absent at the beginning of the relevant discussion. It was not possible to determine on the balance of probabilities exactly what had been said and thus the applicability of the exemption to the definition of promotion. No breach of the Code was ruled.

A pharmacist practitioner at a general practice complained about the conduct of a representative from Sanofi-Aventis.

COMPLAINT

The complainant stated that during the course of discussions with a representative of Sanofi-Aventis about Lantus (insulin glargine) and Acomplia (rimanobant) he was amazed by the apparent lack of knowledge that the representative possessed about data and evidence behind these products.

With respect to Lantus, the representative briefly showed a flowchart from the American Diabetic Association (ADA) and claimed that this advised the use of basal insulins such as Lantus second line to metformin in type 2 diabetics. The complainant had since found this flowchart online; those present were not allowed a close look at this information at the meeting. While this was a recommendation, it was actually one of three interventions advised. The text on the same page as the flowchart also stated 'Early initiation of insulin would be a safer approach for individuals presenting with weight loss, more severe symptoms, and glucose values >250-300 mg/dl'. This was not the impression given by the representative; in fact it was intimated that basal insulins were being recommended in this advice as second line to metformin for all type 2 diabetics.

Of greater concern was the information given about Acomplia. Again the representative presented information that was not passed around or left to allow a closer look but the complainant was certain that the data came from the RIO-Diabetes study. The representative presented these data showing statistically significant reductions in body weight, waist circumference and improvements in other biological markers including HbA_{1C} and cholesterol. However, he wrongly stated that the patients were newly diagnosed and treatment naïve when in fact all had been on oral therapy for 6 months in randomisation. Conversely, the complainant knew that the SERENADE study was conducted in treatment naïve diabetics, however the trial was currently unpublished and the indication studied remained unlicensed. It seemed that the representative was confused about these separate studies and had presented data from the two as if they were one and the same.

The representative then stated that other practices were, based on these data, using Acomplia as a third line hypoglycaemic medicine in diabetics, in place of glitazones. To the complainant's knowledge, and having referred to the current summary of product

characteristics (SPC), he did not believe that Acomplia was licensed as a hypoglycaemic and he did not think it should be promoted on this basis.

The complainant was greatly concerned about several aspects of this meeting:

- that Acomplia was apparently being promoted outside its existing licence;
- the representative's lack of knowledge and the confused messages about the indications, licence and evidence for his products;
- the representative's lack of knowledge about the Code which explicitly forbade off-licence promotion and demanded high quality.

When writing to Sanofi-Aventis the Authority asked it to respond in relation to Clauses 3.2, 7.2 and 15.2 of the Code.

RESPONSE

With regard to the promotion of Lantus the representative confirmed that he presented from the approved materials and spoke in accordance with the training and written materials that he had received to support these. He was also clear that the complainant asked only one question of clarification during the meeting. Sanofi-Aventis considered that many of the issues raised by the complainant might have been avoided had clarification been sought at the time. Although no material used was left with the complainant, had he requested additional information on the items discussed, this would have been provided.

The complainant had questioned the appropriateness of the use of the ADA/European Association for the Study of Diabetes (EASD) guidelines to support the product's use in type 2 diabetics. This flowchart had been faithfully reproduced from the original published in 2006 and was clearly referenced in the detail aid. The original guideline defined the joint position of the two large diabetes medical associations on the optimal treatment of hyperglycaemia in type 2 diabetics. However, the complainant had not identified this article correctly, and his comments referred to a separate article which referred to this flowchart, rather than to the actual guidelines. Had he asked for the reference, this would have been provided through Sanofi-Aventis' medical information service.

The original guidelines (as referenced in the detail aid) indicated that 'Insulin is the most effective of diabetes medications in lowering glycaemia', and advocated 'Early addition of insulin therapy in patients who do not meet target goals' (ie in the group under consideration). Whilst not disregarding the quotation that the complainant had included from elsewhere, the guidelines were very clear that all patients not at target should be considered for insulin therapy. The poorly controlled group of patients that the complainant referred to was included in the original guidelines, but rather than the statement quoted in error by the complainant that in these patients insulin was a safer choice, the guidelines were more proscriptive in directing that in such 'severely uncontrolled' patients, 'insulin is the treatment of choice', as it was the only agent capable of achieving the rapid control of the disease that was essential. Sanofi-Aventis considered therefore that it was consistent with the guidelines that insulin be considered for all patients above target levels of glycaemic control.

Turning to the representative's use of the flowchart, his role was not to promote the guidelines as such, but to indicate where in the guidelines use of Lantus was appropriate. He recalled that he correctly pointed out that a basal insulin (such as Lantus) was an appropriate choice in these patients. As above, Sanofi-Aventis considered that this did not misrepresent the intent of the original guidelines, and that placing Lantus within this context was appropriate promotion in terms of where in practice the product could be used. This was consistent with the training and briefing material that the representative had received.

With regard to the promotion of Acomplia, Sanofi-Aventis noted that the complainant had wrongly identified the study that was discussed during the meeting and his comments about the RIO-Diabetes study were therefore in relation to an incorrect reference. Again, had he asked for clarification at the meeting, the study would have been identified as the SERENADE study. The complainant's comments about the representative misrepresenting the data were therefore confounded by this error. The representative's description of the patient population was correct and consistent with the promotional information - the study was performed in patients with untreated type 2 diabetes, not those who had received oral therapy for at least 6 months. It was clear that the representative made an accurate representation of the materials available to him; any confusion had arisen from the complainant's subsequent misinterpretation and this could easily have been resolved through enquiry at the time of the discussion.

The complainant then questioned the appropriateness of the inclusion of data from the SERENADE study in support of Acomplia, noting that this was in the treatment of diabetes, an unlicensed indication. Whilst the study examined an unlicensed indication, the data used to support Acomplia were restricted to, and entirely consistent with, that which was relevant to the marketing authorization. Specifically, this study was not presented in relation to the treatment of diabetes; the effects demonstrated were limited to those contained within the product licence, namely the effects on obesity (weight and waist circumference) and its associated risk factors (glycaemic control and HDL-cholesterol and triglyceride levels). Likewise, the data presented was that of a subset of patients in the study with a body mass index (BMI) >27kg/m^2, deliberately so as to be in accordance with the marketing authorization. As this study was not yet published, the referenced data on file that supported its inclusion was provided. This was freely available on request and was limited to the particulars of the marketing authorization described above so as to avoid the impression that this study was being used to prompt enquiries on an unlicensed indication.

Finally, it was reported that the representative had referred to the use of Acomplia in other local practices. In this regard the representative clearly remembered that in response to the complainant asking where Acomplia fitted in the treatment of diabetes he had replied that local practices used Acomplia in patients with type 2 diabetes in which weight loss was considered to be appropriate. The complainant then asked if it was being used in place of other medicines, to which the representative replied that some local practices used Acomplia in place of a glitazone. Sanofi-Aventis considered that it was clear that this information was specifically solicited by the complainant and as such the representative had acted appropriately in responding to the request by sharing his knowledge. Providing such information in response to a direct request would be expected; the complainant appeared to have confused this with unsolicited promotion.

In summary, Sanofi-Aventis believed the representative was well informed, well trained and conscientious and he had consistently performed to high standards. It was clear that the representative had used his materials appropriately during his meeting with the complainant, and that these and associated briefing materials were consistent with the requirements of the Code.

Sanofi-Aventis considered that high standards had been maintained throughout and, in particular, that breaches of Clauses 3.2, 7.2 and 15.2 had not occurred.

The response from Sanofi-Aventis was sent to the complainant and his comments invited.

COMMENTS FROM THE COMPLAINANT

The complainant considered that Sanofi-Aventis' response highlighted that the complaint questioned the appropriateness of the use of the ADA/EASD guidelines in the promotion of Lantus. The complainant believed the comment had been misconstrued. He had not questioned the use of these guidelines in general but the way that they were presented. The flowchart provided clearly indicated three treatment alternatives (basal insulin, sulphonylurea or glitazone) for patients failing to reach an HbA_{1C} target of 7% or below while implementing lifestyle interventions and taking metformin. Each intervention was indicated with an advantage (most effective, least expensive and no hypoglycaemia respectively). Treatment choice within the NHS was therefore a clinical decision based on the patients' condition and an assessment of the cost-efficacy of each option with consideration of currently available resources.

That only one of the treatment options was discussed without it being made clear that there were three misrepresented the data. Additionally, while the complainant accepted that the reference was detailed in the promotional aid he noted again that, on the day, those present were not allowed closer examination of the material nor were they left with a copy. It was clear that the representative was not intent on leaving any information behind.

Finally, with respect to the discussion about Accomplia, the complainant noted that in his complaint he had raised the RIO-Diabetes Study. Sanofi-Aventis's response correctly noted that the data represented were from the SERENADE study and not the RIO-Diabetes study. The complainant was surprised that the representative did not correct him when he raised the RIO-Diabetes study during the discussion, even more so given that the detail aid made several references to the SERENADE study as a source for the data. Apparently, the representative was not aware of this or chose to ignore this fact in the conversation.

The complainant noted that Sanofi-Aventis had submitted that the data were presented in line with the current marketing authorization and not presented in relation to diabetes. Despite this assertion the detail aid made it very clear that the SERENADE study was conducted in overweight patients with type 2 diabetes who were inadequately controlled! Additionally, in discussion the representative specifically referred to patients with diabetes (following on from the discussion about Lantus) and diabetes medicines. The complainant also noted page headings in the detail aid which read 'In overweight patients with type 2 diabetes…' and 'Acomplia significantly improves HbA_{1C} compared with placebo' respectively. As these pages were adjacent to each other, the complainant considered that this left the casual reader with the impression that Acomplia could be used to reduce HbA_{1C}. This became even more apparent when comparing the briefing document (prepared in February 2007) with the actual detail aid (prepared in March 2007) from which it would be noted that the claim 'Acomplia significantly reduces weight and waist circumference compared to placebo' had been dropped from the blue header areas in the detail aid. Had this been left in the header area perhaps the detail aid would be less likely to mislead readers.

The complainant noted that the representative claimed he made specific queries about what other practices were doing and where they were using Acomplia in patients with type 2 diabetes. The complainant stated that he must make it clear that he had left the meeting and returned to hear the representative talking about the use of Accomplia instead of glitazone. He therefore sought clarification of the representative's comments whereupon he was told that Acomplia could be used in place of hypoglycaemics and in fact this was being done in other practices locally.

The complainant would never allow his clinical practice to be steered by what other practices were doing. The practice was steered by evidence-based medicine and the complainant was therefore not interested in what other surgeries were doing. The clarification the complainant sought was based on his surprise that Acomplia was apparently touted as an alternative to hypoglycaemics. Furthermore, the complainant had previously noted that representatives always handled conversations about off licence usage very cautiously. It was normal during this type of

discussion to be reminded several times that the company, based on the current marketing authorization, could not endorse such use of the medicine. At no time did the representative mention that such use would be outside the marketing authorization nor did he state that Sanofi-Aventis could not support such use.

Finally, the complainant advised that a diabetes practice nurse and two doctors were also present at the meeting. The complainant had discussed Sanofi-Aventis' response with them, with a view to providing as detailed a response as possible. All three had stated that the representative had left them with the impression that Acomplia could be used to reduce HbA_{1C} in patients with type 2 diabetes. This was particularly clear in their minds as all three of them were confused by this marketing message as they knew Acomplia was licensed as an adjunctive treatment for obesity, not a recognised hypoglycaemic.

FURTHER COMMENTS FROM SANOFI-AVENTIS

Sanofi-Aventis was disappointed that only now the complainant made it known that he was not present for the entire duration of the meeting – this added considerable confusion as to how his perception of the discussion might have been affected. Specifically, the representative was very clear that he placed the Acomplia information in the context of the SERENADE study, which the complainant appeared to be disputing despite the fact that he missed part of the discussion.

Finally, the complainant questioned the impression that Acomplia could be used to 'to reduce HbA_{1C} in patients with type 2 diabetes.' Sanofi-Aventis noted that the marketing authorization for the product stipulated the primary effect as weight loss but included this additional benefit for patients BMI>27kg/m^2 with type 2 diabetes and had acknowledged that promotion of these benefits in addition to the effects on weight was consistent with the marketing authorization. Discussion in this context was not 'use outside the marketing authorization' as the complainant alleged. The promotional campaign for Acomplia positioned the product on this basis – weight loss was always positioned as the primary effect in all materials and any additional effects on risk factors were positioned second to these and always shown in conjunction with the primary effect. The complainant was very clear after the meeting that all staff were aware of the product's primary effect as a treatment for obesity indicating that promotion was effective at conveying this message. It appeared that the impression left of the effect on glycaemic control was additional to the effects on weight rather than in isolation, which remained consistent with the marketing authorization and the promotional campaign, which the representative had very clearly indicated in his comments above.

PANEL RULING

The Panel noted that the complaint had been submitted promptly; the meeting took place on 19 April, the complaint was dated 20 April and was received by the Authority 4 days later. Although each party should therefore have a relatively good recollection of the meeting at issue, it was of concern that accounts differed. The Panel noted that the complainant had been absent for part of the meeting.

The Panel noted the complainant's allegation that during the discussion on Lantus, only one of the three treatment options featured on the ADA/EASD guideline had been discussed and it was not made clear that there were three options. Further the complainant alleged that the representative implied that basal insulin was recommended in the guidelines as second line treatment for all diabetics. The Panel noted that the guideline as shown in the Lantus detail aid clearly detailed three treatment options for patients who failed to reach an HbA_{1C} target of >7% namely; 'Add basal insulin - most effective'; 'Add sulphonylurea - least expensive'; or 'Add glitazone - no hypoglycaemia'. The Panel noted the representative's statement that 'At no point during the Lantus discussions regarding ADA/EASD guidelines did I state or imply that basal insulin was the only option available to them, I clearly stated that it was another option available'. The representatives' briefing material however recommended that representatives focused on the left hand side of the page (the basal insulin option) and led discussion around the positioning of basal insulin. Nonetheless there was no implication in the briefing material that basal insulin was the only option mentioned in the guideline; it was referred to as 'a treatment'. The Panel also noted that the representative also denied that he had intimated that basal insulins were recommended as second line treatment to metformin for all diabetics. The Panel noted the parties' submissions on this point. The Panel considered that it was impossible in such circumstances to determine on the balance of probabilities exactly how the guideline had been presented. No breach of Clauses 7.2 and 15.2 was thus ruled.

The Panel noted each party's submission in relation to the Acomplia data. The representative stated that he had made it clear that he was discussing the SERENADE data and not the RIO-Diabetes study. The Acomplia detail aid clearly referred to the SERENADE study. It appeared that the complainant was concerned that he in error had referred to the RIO-Diabetes study but that this error had not been corrected by the representative. It was impossible to determine on the balance of probabilities what had been said and the Panel thus ruled no breach of Clauses 7.2 and 15.2.

The Panel noted the allegation that Acomplia had been promoted outside of its marketing authorization. The Panel noted that Acomplia was licensed as an adjunct to diet and exercise for the treatment of obese patients (BMI>30kg/m^2) or overweight patients (BMI>27kg/m^2) with associated risk factors, such as type 2 diabetes or dyslipidaemia. The Panel noted that it was not unacceptable to mention the benefits which flowed from using a product for its licensed indication so long as any such discussion was placed firmly within the context of the product's licensed indication. The Panel noted that the detail aid referred to

overweight patients. The relevant representatives' briefing material began 'Identify overweight patients with type 2 diabetes as the patient group we would like to discuss'. This was not unacceptable. Again the Panel considered that it was impossible to determine on the balance of probabilities exactly what had been said and ruled no breach of Clauses 3.1, 7.2 and 15.2.

The Panel noted that according to both parties the discussion of Acomplia had included mention of glitazones. Both parties also agreed that the complainant had asked a question about this matter. However the parties' accounts differed. In addition the complainant had been absent for the beginning of the relevant discussion. According to the complainant he had returned to the meeting room during a discussion about the use of Acomplia instead of a glitazone and had sought clarification of the representative's comments. The complainant did not provide his understanding of how this discussion had started. According to Sanofi-Aventis in response to a question about Acomplia and diabetics the representative explained that local practices used Acomplia in type 2 diabetics in whom weight loss was appropriate. Thereafter, when asked if it was being used in place of other medicines the representative stated that some local practices had used Acomplia in place of a glitazone. The Panel did not accept the company's suggestion that it could rely on the exemption to the definition of promotion set out in Clause 1.2. If the company's version of the discussion was correct it did not appear that the representative had necessarily been asked about replacement of glitazone with Acomplia.

The Panel noted that representatives could respond to unsolicited questions about the unlicensed use of their products so long as the criteria set out in Clause 1.2 and its supplementary information were satisfied. Representatives should be extremely cautious when responding to such requests. It was difficult for representatives to satisfy the criterion given their role, particularly at a group promotional meeting. Attendees were likely to view the representatives' comments in the context of promotion. The safest course of action was to forward such requests to the company's medical information department.

Whilst there were some similarities the parties' accounts differed. In particular the complainant was absent at the beginning of the relevant discussion. It was not possible to determine on the balance of probabilities exactly what had been said and thus the applicability of the exemption to the definition of promotion. No breach of Clauses 15.2 and 3.1 was ruled.

Complaint received	**23 April 2007**
Case completed	**3 August 2007**