CASE AUTH/2477/2/12

CONSULTANT PHYSICIAN v SANOFI

Conduct of representative

A consultant physician alleged that at a hospital diabetes meeting a Sanofi representative had been unprofessional in that she disparaged Levemir (insulin detemir, marketed by Novo Nordisk Limited), and quoted unpublished evidence. The representative stated that as Levemir had recently failed a non-inferiority trial against Lantus (insulin glargine, marketed by Sanofi) there was no reason clinically why it should be prescribed.

The complainant considered this was poor conduct; there were many conflicting studies in this area and it was unacceptable for a company to make negative comments against another brand.

Lantus was for the treatment of adults, adolescents and children of 6 years or above with diabetes mellitus, where treatment with insulin was required.

The detailed response from Sanofi is given below.

The Panel noted Sanofi's submission that the representative organised the meeting to, *inter alia*, discuss the results of the recent EFFICACY trial, a direct comparison of once daily Lantus vs once daily Levemir in type 2 diabetes. The representative had not used material in her presentation.

The Panel noted that the EFFICACY trial concluded that Levemir could not be claimed non-inferior to Lantus with respect to change in HbA1c. The Panel noted Sanofi's submission that representative briefings made it clear that the EFFICACY trial formed part of a comprehensive story supporting Lantus in the treatment of type 2 diabetes, and was not a stand-alone result to be delivered in isolation. At the meeting in question, however, it appeared that this was the only study discussed with regard to Lantus and that, contrary to the briefings, it was not delivered as part of an integrated Lantus story.

The Panel noted that a key message in representatives' briefing described the EFFICACY study as a 'failed study'. A second briefing document stated that further information regarding EFFICACY 'really confirms the fact that Lantus is the superior once daily basal insulin, and should be the only choice when a once-daily insulin is needed'.

The Panel noted that a summary of the EFFICACY results presented by Sanofi to its representatives contained the subtitle 'New Ammunition – The Efficacy Study'. The fourth slide entitled 'How excited should we be about Efficacy?' provided a link to a video on YouTube of two wildly excited children opening their Christmas presents. The Panel questioned whether this video provided a balanced impression of the significance of the trial results.

Following the trial summary, representatives were instructed to practice how 'you would verbalise the messages from the Efficacy paper' and to 'Focus on the language you would use, and the type of outcomes you are hoping to achieve with different customer groups'. The Panel was extremely concerned that representatives had not been given detailed written guidance on how to describe the EFFICACY data.

The final slide of the presentation, entitled 'Lantus Key Message Summary', contained a venn diagram of three inter-locking circles labelled 'Effective HbA1c Control', 'Simplicity' and 'Reassurance for You and Your Patients', respectively. A speech bubble from the 'Simplicity' circle stated 'Lantus is the only true once daily basal insulin'.

The Panel noted that the parties' accounts of what was said at the meeting differed. It was difficult in such circumstances to determine where the truth lay. A decision had to be made on the available evidence. Sanofi submitted that the representative did not tell those present that 'there is no reason clinically why you should prescribe Levemir' nor challenge their prescribing. However, given the statement in the representatives' briefing that Lantus was the only choice when a once daily insulin was required, that the representatives were encouraged to use their own words to communicate the results of the EFFICACY 'message' and the impression given from the YouTube video, the Panel considered that, on the balance of probabilities, the representative had misleadingly implied that there was no clinical reason to prescribe Levemir. A breach of the Code was ruled. The implication could not be substantiated and a further breach of the Code was ruled. The indication for Levemir was, *inter alia*, as part of a basal-bolus insulin regimen once or twice daily depending on patients' needs, and to imply otherwise disparaged the medicine. The Panel further considered that the implication that there was no clinical reason to prescribe Levemir was also disparaging. A breach of the Code was ruled.

The representative in question had not maintained high standards and a breach of the Code was ruled. The claim in representatives' briefing that Lantus 'should be the only choice when a once-daily basal insulin is needed' advocated a course of action that was likely to be in breach of the Code. In addition the Panel noted its critical comment on the representatives' briefing materials above and considered that separately and cumulatively they advocated a course of action likely to be in breach of the Code. A breach of the Code was ruled. The Panel considered that by briefing its representatives that Lantus was the only choice when a once daily insulin was required and by failing to provide adequate written guidance to representatives on how to describe

the EFFICACY study, Sanofi had not maintained high standards and a breach of the Code was ruled.

A consultant physician complained about the conduct of a Sanofi representative at a meeting at a hospital diabetes centre on 25 January.

Sanofi marketed Lantus (insulin glargine) for the treatment of adults, adolescents and children of 6 years or above with diabetes mellitus, where treatment with insulin was required.

COMPLAINT

The complainant alleged that the representative had been unprofessional in that she disparaged Levemir (insulin detemir, marketed by Novo Nordisk Limited), and quoted unpublished evidence. The representative stated (not exact words) that Levemir had recently failed a non-inferiority trial against Lantus and so there was no reason clinically why Levemir should be prescribed.

The complainant considered this was poor conduct as there were many conflicting studies in this area; with less experience the complainant considered that she would have taken the representative at her word and perhaps been influenced not to prescribe Levemir again. The complainant considered that it was acceptable for a company to promote its brand but not by negative comments against the other brand. When the complainant tackled the representative about this she was quite sure that she stood by her word.

In a further letter, the complainant stated that the representative did not use any materials to back up her claims. The complainant challenged the representative stating that she considered it poor practice to talk negatively about a competitor brand. The representative replied that she could do this as it was factual information.

The complainant stated that the representative spent the rest of the meeting demonstrating aspects of a new [blood glucose] meter the company had developed. Following the meeting one of the senior nurses asked the representative for more information about the claim about the inferiority trial for Levemir vs Lantus and she was given a link to some research studies on the Novo Nordisk clinical trial database.

When writing to Sanofi the Authority asked it to respond in relation to Clauses 7.2, 7.4, 8.1, 9.1, 15.2 and 15.9 of the Code.

RESPONSE

Sanofi submitted that the complaint arose following a meeting held a hospital diabetes centre in January 2012 between one of its sales representatives and a group of health professionals. The meeting was set up to share some new data, to discuss and demonstrate Sanofi's new blood glucose meter and to provide an important update on a recent supply issue with one of Sanofi's products.

Sanofi submitted that the representative presented data from the EFFICACY [Effect of Insulin Detemir and Insulin Glargine on Blood Glucose Control in Subjects with Type 2 Diabetes] study recently reported by the study sponsor Novo Nordisk. The representative stated that once daily Levemir had failed to demonstrate non-inferiority compared with once daily Lantus in a recent, and yet unpublished, study. One of the health professionals present challenged this and the representative gave a factual answer based on the available evidence.

Sanofi submitted that the representative had a clear recollection of the meeting and considered that she factually presented the evidence comparing the two products and refuted the allegation that she had disparaged Levemir. Sanofi considered it was to be expected that during the course of promoting a product comparisons with other products would be made. Highlighting advantages over a competitor could not be deemed to be disparaging in this case.

The representative then went on to discuss the other topics and left the meeting. Following the meeting one of the attendees asked the representative for links to the study discussed and the representative supplied links to two publicly available websites where the results of the unpublished study could be found. Sanofi noted that the customer did not request substantiation of the claims made in the call. Had this been the case, the customer would have been provided with a copy of data on file related to the study.

Sanofi confirmed that the representative in question had passed the ABPI Representatives' Examination.

Sanofi submitted that the representative's manager had attended a number of field visits with the representative before and after the meeting in question. In his view the representative had been professional in her presentation of these data in all calls he had witnessed. Furthermore, in these calls the data in question were presented in a balanced manner. The manager considered that it would be highly unlikely for the representative's conduct to be anything other than professional or for the data to have been presented in a different way in the meeting in question.

Sanofi submitted that the EFFICACY study compared the use of Lantus and Levemir in type 2 diabetes when used once daily. Sanofi considered that it was appropriate to present these findings on the basis that this was a significant clinical question and EFFICACY was the only randomised clinical trial to have assessed the effects of the two insulins when used in this manner. The study was not given undue emphasis in the sales materials used by representatives.

Clinical relevance

Sanofi submitted that once daily use of insulins was an important clinical consideration. Clinical trial experience of the two products had typically demonstrated that Levemir could achieve similar

glycaemic control to Lantus but that this often required twice daily injection at higher doses than Lantus and resulted in a greater number of injection site reactions. These had financial and personal implications for both payer and patient.

Sanofi stated that the significance of once vs twice daily injections had similarly been recognised by the National Institute for Health and Clinical Excellence (NICE), with guidance for long-acting insulin analogues being restricted, except for specific circumstances including where 'the person needs assistance from a carer or health professional to inject insulin, and use of a long-acting insulin analogue (insulin detemir, insulin glargine) would reduce the frequency of injections from twice to once daily'.

Sanofi considered that to compare the effect of the two products when used in a strictly once daily setting was therefore an important and clinically relevant concern.

Evidence base

Sanofi submitted that the nature of the evidence from the EFFICACY study was described below in full in response to the requirements of Clause 7.4 of the Code. An equally important consideration, however, was whether the use of this represented the totality of evidence available, or was unnecessarily selective.

To address this question, Sanofi searched MEDLINE (up to week 2 February 2012); 27 articles which referred to both insulins and once daily therapy were identified and once limited to 'clinical trials' 13 remained. These 13 abstracts were reviewed and after excluding one study which compared the colour of injection devices, two uncontrolled observational cohorts and three pharmacodynamics studies, seven randomised clinical trials comparing the efficacy of the two insulins were identified.

Sanofi stated that in all seven studies Levemir was used twice daily, or once or twice daily according to patient need. No study was identified in which once daily Lantus and Levemir were compared. As expected (due to the absence of publication) the EFFICACY study was not identified by the search.

Sanofi also searched the Cochrane Library and a relevant systematic review from July 2011 was identified; 'Insulin detemir versus insulin glargine for type 2 diabetes mellitus' (a copy was provided). Sanofi submitted that this review contained only four randomised clinical trials comparing the two insulins. These four trials were all identified within the MEDLINE search above, and all four included the use of Levemir twice daily. Sanofi noted that a high risk of bias which arose from this difference in dosing regimen was also recognised for each of the four studies.

Finally, and as the EFFICACY study was only identified through being reported within the National Institutes of Health clinical trial registry, Sanofi searched this to identify any other trials comparing the once daily use of Lantus and Levemir. Only one such further study was identified; 'Weight Gain, Eating Patterns, and Development of Body Composition During Initiation of Basal Insulin Therapy in Patients With Type 2 Diabetes: A Comparison of Insulin Detemir and Insulin Glargine'. Sanofi submitted that this study appeared to compare exclusive once daily use of the two insulins, although the last status report (January 2011) was that recruitment was ongoing, and given a 52 week treatment period results were therefore not available. Regardless, an assessment of glycaemic control by measurement of HbA1c was not recorded as an endpoint, so the study was unlikely to provide supporting or refuting evidence once reported.

In view of these search findings, and of the consistent results of the different methodologies, Sanofi concluded that it was highly likely that the EFFICACY study was the only trial which provided evidence comparing Lantus and Levemir when used once daily.

Emphasis within sales materials

A copy of the current electronic detail aid for Lantus was provided; the first to refer to the EFFICACY study. This had been reviewed to consider whether undue emphasis was placed on the study within the overall context of discussion about Lantus. The e-detail aid consisted of 16 sequential pages. On most pages there was the option to call up an additional page to display supporting data, such as reference details or data tables to illustrate key points in more detail.

Sanofi submitted that within the three page 'Efficacy and ease of use' section, only one page focused on the EFFICACY study, and this allowed just one extra screen of information to be called up to illustrate the primary and secondary endpoints. The EFFICACY study was one of nine trials cited in the sales material to the same level of detail, ie mentioned on at least one page and with at least one screen of further detail available.

Sanofi submitted that representative briefings (a copy was provided) made it clear that although this information was the most recent addition to the Lantus sales message, it formed part of a comprehensive story supporting the place of Lantus in the treatment of type 2 diabetes, not a stand-alone result to be delivered in isolation.

Sanofi was confident that the EFFICACY study had not been given undue prominence within either sales materials or instructions to representatives.

Substantiation and accuracy

Sanofi submitted that although it could not cite a peer-reviewed publication (which was not unexpected given the lack of a positive finding), the facts were capable of substantiation through material placed in the public domain by the study sponsor (Novo Nordisk), in accordance with the recognised principles of clinical trial disclosure. The principle reference was the clinical study report

published on Novo Nordisk's clinical trials website; this provided most of the detail to substantiate the claims made in Sanofi's materials, with the exception of the 95% confidence intervals for key endpoints (including the primary endpoint). This information was therefore supplemented by information disclosed by Novo Nordisk on one of the main public trial registries, the US National Institutes of Health ClinicalTrials.Gov site. The information disclosed there provided the 95% confidence intervals key to interpreting the findings of the study. The information contained in these two sources had been consolidated into a single Sanofi data-on-file reference, which had been examined as required by the Code. A copy was provided.

Sanofi submitted that the complainant had alleged that the representative claimed that Levemir failed to demonstrate non-inferiority compared with Lantus when used once daily. Sanofi considered it was clear from the information provided in the study report that the primary objective of the study was:

> 'To compare the efficacy of insulin detemir given once daily versus insulin glargine given once daily, both treatments in combination with metformin during 26 weeks, in subjects with type 2 diabetes inadequately controlled on metformin treatment with or without one other oral antidiabetic drug (OAD)'

And that the primary objective of the study was not met:

> 'After 26 weeks, [insulin detemir] could not be claimed non-inferior to [insulin glargine] with respect to change in HbA_{1c}'

Sanofi stated that the reason for failing to meet the test on non-inferiority was not provided in the clinical study report, although it was clear that the test that had been applied related to the two-sided 95% confidence interval for the difference in treatment effect for Levemir compared with Lantus. If the upper limit of that confidence interval was to fall below 0.4%, Levemir was to be claimed non-inferior to Lantus in terms of HbA1c with respect to a non-inferiority margin of 0.4%.

Sanofi submitted that the confidence interval for the primary endpoint was however in the information presented on ClinicalTrials.Gov. This confirmed the net mean treatment difference to be a reduction of HbA1c of 0.3003% in favour of Lantus, with a 95% confidence interval of 0.1427 to 0.4580%. This made clear that the upper limit of the 95% confidence interval crossed the 0.4% non-inferiority margin, confirming the failure of Levemir to show non-inferiority compared with Lantus. This disclosure also provided the information that the entire 95% confidence interval remained above 0% (all in favour of Lantus), ie that there was a statistically significant effect in favour of Lantus. This information, along with the key secondary endpoints, both significant and non significant, were presented as the additional page of detail from the EFFICACY study, and were all an accurate representation of the figures available in the two data sources, as reflected in the data-on-file used to support the claims.

Conclusion

Taking all these matters into consideration, Sanofi considered that although the EFFICACY study was a single study comparing the once daily use of Lantus and Levemir, it was the only study that made that comparison. This was a clinically important scenario that required evidence and the material was presented without undue emphasis in promotional materials, or with any direction in representative briefings to be presented with undue emphasis.

Sanofi also considered that all claims relating to the EFFICACY study, made both verbally by the representative and written in the sales material, were a fair and accurate interpretation of the facts available, and all were substantiated by the two sets of data disclosed by Novo Nordisk. Sanofi therefore denied any breach of Clauses 7.2 or 7.4.

Sanofi submitted that the data demonstrated that once daily Levemir failed to show non-inferiority compared with once daily Lantus in the treatment of type 2 diabetes.

Sanofi considered that the information it had provided outlined the conduct of the representative in the call and showed how the data in question were represented in sales material. Sanofi considered that it had accurately represented the data from the study which showed an advantage for Lantus and this was not disparaging. Sanofi denied a breach of Clause 8.1.

A copy of all representative briefing material related to the use of the EFFICACY study was provided. Sanofi submitted that representatives were first briefed about this study in October 2011 to enable them to respond to customer enquiries. They were briefed again in December and given a pre-recorded presentation of the data to enable them to proactively discuss these new data with customers. The representatives were trained again when they received the e-detail aid referred to above.

During the course of its investigation Sanofi had identified that, regrettably, one presentation to the sales team had not been certified. It was submitted into the review process and had been reviewed and approved by two final signatories but the formal certification step was not completed. Sanofi thus accepted a breach of Clause 15.9 in relation to this one item and with that a Clause 9.1.

In light of the evidence presented above related to the meeting, Sanofi denied a breach of Clause 15.2.

Following a request for further information, Sanofi submitted that the representative in question had set the agenda for the meeting, to include new Lantus/Levemir comparative data, a demonstration of Sanofi's new blood glucose meters and an update on the supply situation of another Sanofi product. On opening the call the representative explained that

the basis of the new data was that Levemir had failed to meet non-inferiority in a trial against Lantus. The flow of the intended call was then stopped by the complainant who stated 'You are not allowed to use the words inferior and non-inferior. You should be saying superior to…'. Sanofi submitted that there was no question from the complainant for the representative to respond to.

Sanofi submitted that the representative then continued to explain the EFFICACY study, its design and primary endpoint of non-inferiority to Lantus, going on to outline the outcomes of the trial and results leading to the conclusion that Levemir did not reach non-inferiority to Lantus, making it clear why she had used the words inferior and non-inferior rather than superior. The representative made it clear that the data was not published in a peer reviewed journal, however it was available at both the Novo Nordisk website and the ClinicalTrials.gov website.

Sanofi stated that there were no further questions around the EFFICACY study or any other studies involving Lantus or Levemir. This then led into a discussion about the use of NPH [neutral protamine Hagedorn], and NICE guidelines. The representative did not tell the group 'there is no reason clinically why you should prescribe Levemir' nor challenge their prescribing. The representative then demonstrated Sanofi's two new blood glucose meters.

Sanofi submitted that the representative did not use any material at the meeting but left a leavepiece relating to the blood glucose meter.

PANEL RULING

The Panel noted that the complainant had alleged that the representative had stated or implied that Levemir had recently failed a non-inferiority trial against Lantus and so there was no reason clinically why Levemir should not be prescribed.

The Panel noted Sanofi's submission that the meeting at issue was organised by the representative in order to discuss the results of the EFFICACY trial, demonstrate Sanofi's new blood glucose meters and provide an update on supply issues for one of Sanofi's products. Sanofi had submitted that although the representative had presented data from the EFFICACY trial she had not used any material to do so.

The Panel noted that according to Novo Nordisk's published clinical trial synopsis, EFFICACY was a randomized, open label, non-inferiority trial. Its primary objective was to compare the efficacy of once daily Levemir vs once daily Lantus, each in combination with metformin, over 26 weeks in type 2 diabetics inadequately controlled on metformin with or without one other oral antidiabetic medicine. Details of the confidence intervals were provided. The authors concluded that after 26 weeks, Levemir could not be claimed non-inferior to Lantus with respect to change in HbA1c. A comparative analysis between treatment arms showed a significant difference in favour of the Lantus arm for the proportion meeting HbA1c targets (both ≤7% and ≤6.5%). No significant differences between treatment arms were found when comparing the same targets but in the absence of hypoglycaemia. The statistical significance of some differences was not clear.

The Panel noted Sanofi's submission that representative briefings made it clear that although the results of the EFFICACY trial were the most recent addition to the Lantus sales message, it formed part of a comprehensive story supporting the place of Lantus in the treatment of type 2 diabetes, and was not a stand-alone result to be delivered in isolation. At the meeting in question, however, it appeared that this was the only study discussed with regard to Lantus and that, contrary to the briefings, it was not delivered as part of an integrated Lantus story.

The Panel noted that a key message in a representatives' briefing document on the EFFICACY study, issued in October 2011 for reactive use only, described it as a 'failed study'. The Panel further noted that a second internal briefing was issued in December 2011 to all field-based promotional teams from the Sanofi brand lead, insulins, entitled 'EFFICACY study Training'. It stated that Sanofi had '…..developed and tested key messages from this study and integrated these in to a strengthened Lantus vs Levemir story which you will get to familiarise yourself with at Cycle 1 meeting'. The brief further stated that in the past week further information had been released regarding EFFICACY which 'really confirms the fact that Lantus is the superior once daily basal insulin, and should be the only choice when a once-daily insulin is needed'.

The Panel noted that a summary of the EFFICACY results presented at Cycle meeting 1 contained the subtitle 'New Ammunition –The Efficacy Study'. The fourth slide entitled 'How excited should we be about Efficacy?' provided a link to a video on YouTube of two wildly excited children opening their Christmas presents. The Panel questioned whether this video provided a balanced impression of the significance of the trial results.

The summary stated whether differences were statistically significant and that no p values were provided in the available data.

Following the trial summary, a slide headed 'Group Practice' instructed the representatives to form in to account teams and take five minutes to familiarise themselves with how the data was represented. Following this, the representatives were to use the remaining 25 minutes in pairs practicing how 'you would verbalise the messages from the Efficacy paper' and to 'Focus on the language you would use, and the type of outcomes you are hoping to achieve with different customer groups'. The Panel was extremely concerned that the representatives had not been given detailed written guidance on how to describe the data from the EFFICACY study.

The final slide of the presentation, entitled 'Lantus Key Message Summary', contained a venn diagram

of three inter-locking circles, each containing one of the statements 'Effective HbA_{1c} Control', 'Simplicity' and 'Reassurance for You and Your Patients'. A speech bubble coming from the 'Simplicity' circle stated 'Lantus is the only true once daily basal insulin'.

The Panel noted that the parties' accounts of what was said at the meeting differed. It was difficult in such circumstances to determine where the truth lay. A decision had to be made on the available evidence. Sanofi submitted that the representative did not tell those present that 'there is no reason clinically why you should prescribe Levemir' nor challenge their prescribing. However, given the statement in the representatives' briefing in relation to Lantus being the only choice when a once daily insulin was required, encouragement at the Cycle meeting 1 of the representatives to use their own words to communicate the results of the EFFICACY 'message' and the impression given to representatives from the YouTube video, the Panel considered that, on the balance of probabilities, the representative had misleadingly implied that there was no clinical reason to prescribe Levemir. A breach of Clause 7.2 was ruled. The implication could not be substantiated and a breach of Clause 7.4 was ruled. The indication for Levemir was, *inter alia*, as part of a basal-bolus insulin regimen once or twice daily depending on patients' needs, and to imply otherwise was disparaging to the medicine. In addition the Panel considered that the implication that there was no clinical reason to prescribe Levemir was also disparaging. A breach of Clause 8.1 was ruled.

The representative in question had not maintained high standards and a breach of Clause 15.2 was ruled. The claim in the representatives' briefing document that Lantus 'should be the only choice when a once-daily basal insulin is needed' advocated a course of action that was likely to be in breach of the Code. In addition the Panel noted its critical comment on each of the representatives' briefing materials above and considered that separately and cumulatively they advocated a course of action likely to be in breach of the Code. A breach of Clause 15.9 was ruled. The Panel considered that by briefing its representatives that Lantus was the only choice when a once daily insulin was required and by failing to provide adequate written guidance to representatives on how to describe the EFFICACY study, Sanofi had not maintained high standards and a breach of Clause 9.1 was ruled.

Complaint received **3 February 2012**

Case completed **17 April 2012**