CASE AUTH/2141/7/08

NOVO NORDISK v SANOFI-AVENTIS

Promotion of Lantus

Novo Nordisk complained about the promotion of Lantus (insulin glargine) by Sanofi-Aventis. The materials at issue were: four leavepieces and a mailer. Novo Nordisk marketed Levemir (insulin determir).

A '24 hour efficacy' claim appeared as part of the Lantus product logo in one of the leavepieces and as a discreet claim 'Once daily – provides 24-hour efficacy' in all of the other materials.

Novo Nordisk was concerned about the substantiation of this claim and noted the Appeal Board ruling in Case AUTH/2028/7/07 which stated that results from a clamp study (Lepore *et al* 2000) could not substantiate the efficacy of insulin in terms of glycaemic control. This was also true for other comparable clamp trials (Porcellati *et al* 2007a and Porcellati *et al* 2007b) provided by Sanofi-Aventis to substantiate this claim. Novo Nordisk agreed with Sanofi-Aventis that the efficacy of a medicine was its capacity to produce a desired effect. However, it strongly disagreed with the argument that the lack of qualification of this term (ie efficacy) made it capable of substantiation by results from clamp trials. In fact the desired effect of an insulin was to provide proper glycaemic control by reducing blood glucose levels in patients. The undertaking in Case AUTH/2028/7/07 clearly prohibited the use of the claim '24-hour control' or similar. Thus Novo Nordisk believed that the claim of '24-hour efficacy' was in breach of the Code.

In relation to the same claim used alongside a graph from Porcellati *et al* (2007b), Novo Nordisk was concerned that Sanofi-Aventis had cherry-picked the only clamp trial which revealed a significant difference in terms of duration of action between Lantus and Levemir. Other data, of which details were given, had been overlooked. Novo Nordisk alleged that the claim, based on a comparison from a single trial which provided contradictory results, whilst disregarding all other published evidence, misled health professionals and disparaged Levemir.

The detailed response from Sanofi-Aventis is given below.

The Panel noted that in Case AUTH/2028/7/07 claims for '24-hour control' or '24-hour glycaemic control' for Lantus had been considered to not be capable of substantiation and exaggerated and misleading in that regard by the Appeal Board. Breaches of the Code had been ruled.

In Case AUTH/2028/7/07 the data submitted in support of the claims had demonstrated the 24-hour duration of action of Lantus, not its efficacy in terms of glycaemic control. In the Appeal Board's view, control, in the context of diabetes, referred to glycaemic control ie the maintenance of blood glucose between set parameters. The Appeal Board noted that Lantus was a basal insulin designed to provide a background, constant suppression of blood glucose. Sanofi-Aventis had submitted that no type 1 diabetic would be controlled solely on Lantus and only about half of type 2 diabetics would be controlled on a combination of Lantus and oral agents. Most diabetics would thus not be 'controlled' with Lantus and would require short-acting insulin to cope with post prandial glucose peaks.

The Panel noted that the claim now at issue was '24-hour efficacy'. In the Panel's view the claim would be read by prescribers in the context of a basal insulin. Prescribers would take it to mean that Lantus provided a constant suppression of blood glucose over 24-hours ie that it had a 24-hour duration of action.

The Panel noted that the claim 'once daily – provides 24-hour efficacy' appeared in two leavepieces immediately under the prominent headline 'Lantus – control without compromise for your diabetes patients'. In that context the Panel considered that '24-hour efficacy' implied '24-hour control' and was thus in breach of the undertaking given in Case AUTH/2028/7/07. A breach of the Code was ruled. This ruling was appealed by Sanofi-Aventis.

The Panel considered that an undertaking was an important document. It included an assurance that that all possible steps would be taken to avoid similar breaches of the Code in future. It was very important for the reputation of the industry that companies complied with undertakings. In breaching its undertaking the Panel considered that Sanofi-Aventis had not maintained high standards and had brought discredit upon, and reduced confidence in the industry. Breaches of the Code were ruled including Clause 2. These rulings were appealed by Sanofi-Aventis.

The Appeal Board noted that the intended audience for the two leavepieces were diabetes nurse specialists, diabetologists and GPs with an interest in diabetes. The Appeal Board considered that although the claim 'Once-daily – provides 24-hour efficacy' appeared below the claims 'Lantus-control without compromise for your diabetes patients', given the audience it would not be taken to imply '24-hour-control' but a claim for duration of action.

The Appeal Board had some concerns about the claim and its context but on balance decided that Sanofi-Aventis had not breached its undertaking given in Case AUTH/2028/7/07. The Appeal Board ruled no breaches of the Code including Clause 2.

In one leavepiece, the claim '24-hour efficacy' was used as part of the Lantus product logo. Although page 2 of the leavepiece included the claim 'Lantus can enable people to improve their glycaemic control', the Panel did not consider that in the context in which it appeared, '24-hour efficacy' implied '24-hour control' as in the leavepieces considered above. In another leavepiece the claim 'once daily – provides 24-hour efficacy' appeared beneath the claim 'Lantus – established efficacy ….' and in the mailer the claim '24-hour efficacy' appeared as a headline claim above data relating to duration of action. The Panel noted its comments above regarding a prescriber's expectation of Lantus and the view that would be taken of the claim '24-hour efficacy' in the context of a basal insulin. The Panel considered that there was data to show that Lantus had a 24-hour duration of action; section 5.1 of the SPC included a graph which showed that the activity profile of Lantus was smooth, peakless and almost constant between 9 and 24-hours in type 1 diabetics. The Panel considered that in the context in which it appeared in two of the leavepieces and the mailing, the claim '24-hour efficacy' could be substantiated and no breach of the Code was ruled.

The Panel noted that the leavepiece and the mailing both featured a graph depicting plasma glucose levels over time with Lantus and Levemir (Porcellati 2007b). The graph of results generated after two weeks of treatment and showed that in type 1 diabetics Lantus suppressed plasma glucose for 24-hour post injection whereas blood glucose levels started to rise in the Levemir group 15 hours post dose.

The Panel noted that Heise and Pieber (2007) had reported that in the clinically relevant range of 0.35-0.8U/kg the duration of action for Lantus and Levemir was close to 24 hours in type 1 diabetes. Heise and Pieber had further commented that the data from Porcelatti was an outlier. Given data from Plank *et al* (2005), and the comments from Heise and Pieber, the Panel considered that the graph at issue did not represent the balance of evidence with regard to the duration of action of Levemir in type 1 diabetes. Furthermore, the graph implied a duration of action of only 15 hours ie when plasma glucose levels began to rise whereas the authors themselves reported the duration of action to be 17.5 hours. The graph did not include a threshold blood glucose level beyond which the insulin could be regarded as no longer acting. The Panel considered that the graph was misleading and a breach of the Code was ruled. The Panel further considered that the graph disparaged Levemir and a breach of the Code was ruled. These rulings were appealed by Sanofi-Aventis. Although noting its rulings above the Panel did not consider that high standards had not been maintained. No breach of the Code was ruled.

The Appeal Board considered that the results depicted in the graph at issue were not inconsistent with the products' SPCs. Lantus should be administered once daily. The recommended initiation of Levemir in combination with oral antidiabetic agents was once daily. When Levemir was used as part of a basal-bolus regimen it should be administered once or twice daily based on individual patient needs. The Appeal Board noted that the balance of evidence showed that Lantus suppressed plasma glucose for a longer period of time than Levemir.

The Appeal Board did not consider that the graph was either misleading or that it disparaged Levemir. No breach of the Code was ruled.

Novo Nordisk noted that the claim 'In clinical practice, after switching from other treatments, Lantus is associated with a lower risk of hypoglycaemia compared to insulin detemir' appeared in one of the leavepieces and in the mailer.

Novo Nordisk noted that the claim was substantiated by findings from a retrospective GP database analysis (Currie *et al* 2007). The authors compared the reported hypoglycaemic event rate prior to and following initiation of basal Lantus and Levemir (a secondary endpoint of the analysis) and concluded that the risk reduction in hypoglycaemia was significantly greater with Lantus. However, there were some limitations of this analysis which needed to be considered to decide whether the claim, substantiated by this paper, was misleading or not. The authors compared the clinical outcomes of 5,683 patients using Lantus with outcomes of only 694 patients using Levemir. The huge difference in patient numbers obviously reflected the more established clinical experience of using Lantus at that time, ie prescribers were more familiar with its use. Therefore the analysis was biased in favour of Lantus.

Although Currie *et al* analysed the primary endpoint of HbA1c change, and the secondary endpoint of weight change separately in type 1 and type 2 diabetes patients, they failed to follow this fair and highly relevant approach with regard to hypoglycaemia. Further, they failed to differentiate between major and minor hypoglycaemic episodes or episodes that occurred during the day or at night. This lack of clarification raised the question of whether this analysis provided clinicians with any useful findings regarding hypoglycaemia. Defining the types of hypoglycaemic events would be crucial in order to make clinically relevant conclusions from this analysis.

It was well know that hypoglycaemic risk was markedly different in type 1 and type 2 diabetes. Major and minor hypoglycaemic events were more common in type 1 diabetes than in type 2. There

was also agreement in the literature that there was a higher incidence of hypoglycaemic episodes in patients with a more advanced stage of type 2 diabetes ie those requiring more intensive antihyperglycaemic therapy (Cryer *et al* and Zammitt and Frier).

These differences in hypoglycaemic risk could be partially explained by the use of different insulin regimens. Whilst type 1 diabetics almost exclusively used a basal-bolus regimen, in type 2 diabetes basal insulins could be used as part of basal-oral or basal-bolus regimens. Since basal-bolus therapy was a much more aggressive approach to control blood glucose levels, and was usually applied at a considerably more severe stage of type 2 diabetes, it was connected with a significantly higher hypoglycaemic event rate than a basal-oral regimen.

One might reasonably assume that in the case of type 1 diabetes, the only flaw in Currie *et al* was the above mentioned 'familiarity' effect in terms of Lantus, since both preparations were used as part of a basal-bolus regimen. However in type 2 diabetes it had to be presumed that apart from this effect there was at least one more bias in favour of Lantus. Whilst it was not clear from the published paper, it was reasonable to assume that many more patients in the Lantus group would have been treated with basal-oral treatment. In the Levemir group the vast majority of the patients would have been treated with a basal-bolus regimen. This was because Lantus had a licence for both basal-oral and basal-bolus use, whilst Levemir only had a licence for basal-bolus use during the analysed period.

Therefore to compare the hypoglycaemic rate reduction without taking into account the type of diabetes and the insulin regimen for those with type 2 diabetes was misleading. In addition, the fact that information on the use of bolus insulin, readily available from the THIN database, had been clearly overlooked and not taken into account in this analysis was disappointing. The authors simply chose to compare the hypoglycaemic risk reduction in the combined cohort of type 1 and type 2 patients and failed to make any distinction between basal-oral users and basal-bolus users in the type 2 cohort.

The claim at issue was purely based on the results from this flawed analysis. Relevant data from published randomized clinical trials detailed by Novo Nordisk had been overlooked.

Novo Nordisk believed that Sanofi-Aventis had again cherry-picked the results from a retrospective database analysis, which was severely flawed in terms of hypoglycaemic risk analysis, to substantiate the claim. The company had clearly disregarded all the other published evidence which had revealed completely different results. Therefore the claim was inaccurate, unbalanced, unfair, and ambiguous, it was not based on an up-to-date evaluation of all available evidence and disparaged Levemir.

The Panel noted that one leavepiece was specifically about the use of Lantus in type 2 diabetics. The final page featured the claim at issue referenced to Currie *et al* a study which had demonstrated that in a pooled cohort of type 1 and type 2 diabetics, patients switched to Lantus had a lower relative risk of hypoglycaemia than those switched to Levemir. Given the specificity of the leavepiece, however, the Panel considered that a claim based on pooled data from type 1 and type 2 diabetics was misleading. A breach of the Code was ruled. The Panel did not consider that the claim disparaged Levemir and so no breach of the Code was ruled. The Panel noted that use of Currie *et al* and the need to ensure that readers understood that the hypoglycaemia data was from a pooled cohort of patients had been at issue in Case AUTH/2038/8/07. The Panel considered that to again use the pooled data in a way that was misleading meant that high standards had not been maintained. A breach of the Code was ruled. This ruling was upheld by the Appeal Board on appeal by Sanofi-Aventis.

The mailing, 'Why choose Lantus' was not specific as to the type of diabetic patients at issue – the mailing referred to both type 1 and type 2 patients. As in the leavepiece above the claim at issue had been derived from Currie *et al*. The Panel noted that the data was generated when the licence for Levemir did not include management of type 2 diabetes except as part of a basal-bolus regimen. Levemir could now be used as part of a basal-oral regimen and so patients who were less prone to hypoglycaemic attacks could be treated. The pooled cohort of type 1 and type 2 diabetics included in Currie *et al* was thus likely to be different to the mixed group of diabetics that a prescriber might now treat with either Lantus or Levemir and so on that basis the Panel considered that the claim at issue was misleading. A breach of the Code was ruled. This ruling was appealed by Sanofi-Aventis. Although noting this ruling the Panel did not consider that high standards had not been maintained nor that the claim disparaged Levemir. No breach of the Code was ruled.

The Appeal Board noted the mailing, referred to both type 1 and type 2 diabetes patients. As in the leavepiece above the claim at issue had been derived from Currie *et al*. In this instance, however, the Appeal Board considered that as the mailing had referred to both type 1 and type 2 diabetes, the claim based on pooled data from type 1 and 2 patients was not misleading. The Appeal Board ruled no breach of the Code.

Novo Nordisk complained about the promotion of Lantus (insulin glargine) by Sanofi-Aventis. The materials at issue were: four leavepieces (refs LAN07/1333; LAN08/1037; LAN08/1038 and LAN08/1039) and a mailer (ref LAN08/1041).

Novo Nordisk marketed Levemir (insulin determir).

This case was considered under the 2008 Constitution and Procedure. The clauses cited, 2, 7.2, 7.4, 9.1 and 22, were the same in the 2006 Code as the 2008 save for Clause 22 which had been renumbered as Clause 25. Thus the 2008 Code was used.

1 Claim '24-hour efficacy'

This claim appeared as part of the Lantus product logo in one of the leavepieces (ref LAN07/1333) and as a discreet claim 'Once daily – provides 24-hour efficacy' in all of the other materials.

COMPLAINT

Novo Nordisk was concerned about the substantiation of this claim and noted the Appeal Board ruling in Case AUTH/2028/7/07 which stated that results from a clamp study (Lepore *et al* 2000) could not substantiate the efficacy of insulin in terms of glycaemic control. This was also true for other comparable clamp trials (Porcellati *et al* 2007a and Porcellati *et al* 2007b) which were provided by Sanofi-Aventis to substantiate this claim. Novo Nordisk agreed with Sanofi-Aventis that the efficacy of a medicine was its capacity to produce a desired effect. However, it strongly disagreed with the argument that the lack of qualification of this term (ie efficacy) made it capable of substantiation by results from clamp trials. In fact the desired effect of an insulin was to provide proper glycaemic control by reducing blood glucose levels in patients. The undertaking in Case AUTH/2028/7/07 clearly prohibited the future use of the claim '24-hour control' and any similar claim. Thus Novo Nordisk believed that the claim of '24-hour efficacy' was not only in breach of Clause 7.4 of the Code but also of Clauses 2, 9.1 and 22.1.

In relation to the same claim used alongside a graph from Porcellati *et al* (2007b) (LAN/08/1039 and LAN08/1041), Novo Nordisk was concerned that Sanofi-Aventis had cherry-picked the only clamp trial which revealed a significant difference in terms of duration of action between Lantus and Levemir. Sanofi-Aventis had clearly overlooked published results from other clamp trials and a comprehensive review paper which supported a similar duration of action for both. Klein *et al* (2007) demonstrated that duration of action in type 2 diabetes was similar for Lantus and Levemir. Plank *et al* (2005) (duration of action was 19.9 hours at a dose of 0.4U/kg) confirmed that also in type 1 diabetes Levemir had a similar duration of action as Lantus (defined by Lepore *et al*: duration of action was 20.5 hours at a dose of 0.3U/kg). Furthermore Porcellati *et al* (2007b) reported relevant clinical data from the 2-week long treatment period prior to the clamp procedures. During the treatment period, patients used a once daily dose of either Lantus or Levemir as the basal part of their basal-bolus regimen. The blood glucose findings from this treatment period contradicted the findings from the clamp phase of this trial. It would be very difficult to explain how once-daily Levemir, as part of a basal-bolus regimen, provided exactly the same metabolic control as the basal-bolus regimen using once-daily Lantus (in combination with rapid-acting insulin analogues), despite having a substantially shorter duration of action as was suggested by the clamp part of the same trial. Novo Nordisk alleged that the claim, based on a comparison from a single trial which provided contradictory results, whilst disregarding all other published evidence, misled health professionals and disparaged Levemir, in breach of Clauses 7.2, 8.1 and 9.1 of the Code.

RESPONSE

Sanofi-Aventis submitted that this complaint followed Case AUTH/2028/7/07, in which Novo Nordisk complained that claims for, '24-hour control' and 24- hour glycaemic control' in relation to Lantus were not capable of substantiation.

In its original defence of these claims, Sanofi-Aventis provided information from three isoglycaemic clamp studies which demonstrated that Lantus had a duration of action of at least 24-hours:

- Firstly, that a euglycaemic clamp was the appropriate methodology to assess the pharmacokinetics and pharmacodynamics of insulin performed by Lepore *et al*. In a real life setting, a basal insulin was used to maintain a steady background (or fasting) level of blood glucose. The most relevant clinical measure in clamp studies such as Lepore *et al* was the ability of each insulin to keep blood glucose levels below a clinically relevant threshold – typically 150mg/dl (8.3mmol/L). Lepore *et al* demonstrated that at the end of the 24-hour study period the mean blood glucose level for Lantus patients was 141mg/dl, ie below the 150mg/dl threshold that would have indicated that Lantus was no longer effective. As the primary end-point of the study, this result in particular strongly supported the claim that Lantus could be expected to confer 24-hour efficacy, even with the limitation of this study representing only a single dose of Lantus (ie not at steady state as would be the case in clinical practice).

- Secondly, Porcellati *et al* (2007a) assessed the pharmacokinetics and pharmacodynamics of Lantus in the same manner, this time after the first dose and also after seven days of treatment ie at steady state conditions. The clamp assessment on the seventh day was continued for 32 hours as opposed to 24 to better assess the duration of action of Lantus. Even at a low dose of 0.3U/kg, the median duration of action at seven days was again 24 hours.

- Finally, Porcellati *et al* (2007b) assessed the pharmacokinetics and pharmacodynamics of

Lantus in 24 patients with type-1 diabetes using a euglycaemic clamp technique, this time after two weeks of treatment. This study was performed at a dose of 0.35U/kg (approximately 24.5 units for a 70kg man), and again at this relatively low dose all subjects had satisfactory maintenance of glycaemic control at the end of a 24-hour study period performed at steady state conditions.

In Case AUTH/2028/7/07 the Panel and Appeal Board had both agreed that the data supported the claim that Lantus had a 24-hour duration of action. However, the Appeal Board 'considered that a once daily dosage or a 24-hour course of action for a basal insulin did not equate to 24-hour glycaemic control', as a proportion of patients would require additional mealtime insulin to fully control their diabetes. The inability of Lantus alone to provide 'glycaemic control' in all patients with diabetes rendered the statement incapable of substantiation, despite its 24-hour duration of action as a background basal insulin.

In view of this ruling, Sanofi-Aventis withdrew the claim '24-hour control' and replaced it with '24 hour efficacy', now the subject of this complaint (Case AUTH/2141/7/08). The '24-hour efficacy' claim took into account the Appeal Board's ruling together with the agreed robust evidence previously provided to substantiate the 24-hour duration.

Sanofi-Aventis could understand that Novo Nordisk wanted to challenge the change from 'control' to 'efficacy', and responded accordingly in inter-company dialogue. It was disappointing that a large part of the argument made to support this complaint appeared to be an attempt to reopen concerns dismissed in Case AUTH/2028/7/07, as outlined above.

In response to Novo Nordisk's concern that the term 'efficacy' still implied 'control', Sanofi-Aventis made this change and took full note of the Appeal Board's ruling that Lantus was a 'basal insulin designed to provide a background, constant suppression of blood glucose and that it considered that a once daily dosage or a 24-hour course of action for a basal insulin did not equate to 24-hour glycaemic control', with the implication that basal insulin action and glycaemic control could not therefore be considered the same.

The claim '24-hour efficacy' was therefore made in relation to the fact that Lantus demonstrated a 24-hour course of action as a basal insulin - in that it provided the continuous level of insulin required to regulate hepatic glucose production, which occurred at a relatively constant rate. 'Efficacy' referred to this continuous basal insulin effect - the claim '24-hour efficacy' meant '24-hour duration of pharmacodynamic action' (as a basal insulin), and this had already been readily demonstrated in the three clamp studies referred to above. Sanofi-Aventis considered that this claim did not allude to the fact that Lantus would provide full glycaemic control - clinicians who treated diabetes would know that Lantus was a basal insulin intended to provide background insulin cover only, and that mealtime insulin would be required in all patients with type 1 diabetes and a proportion of those with type 2 diabetes.

Sanofi-Aventis noted that Novo Nordisk objected to the fact that the graph reproduced from Porcellati *et al* (2007b) cherry-picked the available data, with a suggestion that Sanofi-Aventis had overlooked Klein *et al* and Plank *et al*. Again, this was disappointing since similar points were made and considered in Case AUTH/2028/7/07.

- Although Novo Nordisk stated that Klein *et al* (key to its original argument) was relevant, the point was made in the paper itself that the methodology was flawed - glucose infusion rate was not an effective measure of an insulin's duration of action (a point considered significant in the original case). This position was again repeated in a review of clamp studies with basal insulin analogues (Heise and Pieber 2007). In both cases the suggestion was that blood glucose concentration over 24-hours was the most appropriate measure to demonstrate duration of action, again a point agreed when this matter was first considered.

- Klein *et al* also suffered from the disadvantage that the methodology was that of a single dose, as opposed to the steady state dosing that was usual in clinical practice. In total, Sanofi-Aventis did not consider therefore that the methodology or conclusions of Klein *et al* were comparable to those of Porcellati *et al* (2007b), and as this presented a like-with-like comparison the allegation of omission was not warranted.

That said, the graph reproduced in the leavepiece (LAN08/1039) and the mailer (LAN08/1041) from Porcellati *et al* (2007b) demonstrated that blood glucose concentrations remained below a threshold level for 24-hours after treatment with Lantus – the most appropriate measure of insulin activity considered by Klein *et al* and Heise and Pieber – whereas blood glucose levels increased after approximately 16 hours with Levemir.

Taking the same measure from Klein *et al*, it appeared that the findings in Klein *et al* were similar to those of Porcellati *et al* (2007b) ie that Lantus demonstrated maintenance of normal blood glucose levels for 24-hours whereas the effects of Levemir appeared to decline after approximately 16 hours, evidenced by the increase in blood glucose levels.

It was difficult to accept that cherry-picking had occurred in reference to Porcellati *et al* (2007b) when Klein *et al* demonstrated such a similar result, at this dose level at least.

- In response to the suggestion that Plank *et al* should also have been quoted, Sanofi-Aventis noted that this study did not compare Lantus and

Levemir. As the promotional item sought to directly compare the two products this did not appear to be relevant to the argument – it was indirect evidence only and not appropriate when a direct comparison of the two products was made.

- Finally, Novo Nordisk submitted that in Porcellati *et al* (2007b) there was a similar level of glycaemic control after two weeks of treatment with both Levemir and Lantus, each once daily, and suggested that this was proof that Levemir had a 24-hour duration of action. Novo Nordisk failed to note, however, that in the 2 week run-in period subjects in the study also received mealtime insulin as required, and that the glycaemic control exhibited could not be attributed to once daily Levemir alone.

In summary, Sanofi-Aventis believed that the claim, '24-hour efficacy' fairly reflected the 24-hour duration of action that the Panel and the Appeal Board had already considered appropriate and that the word 'efficacy', made in respect to the action of Lantus as a basal insulin, was now a fair and appropriate reflection that Lantus did what it was intended to do (provide basal insulin cover) for 24-hours. Sanofi-Aventis considered that the claim could be substantiated, was not misleading and had been amended according to the previous Appeal Board ruling.

Sanofi-Aventis also considered that using Porcellati *et al* (2007b) to demonstrate the 24-hour duration of action of Lantus, and the shorter duration of action of Levemir, was justified as it was the most relevant and only study conducted in the steady state condition, which reflected clinical practice, and whose conclusions were not limited by the methodological concerns identified in Klein *et al*. In view of these facts, Sanofi-Aventis did not believe reference to this study was misleading or misrepresentative of clinical data.

Sanofi-Aventis considered that high standards had been maintained throughout and that no breach of the Code had occurred.

PANEL RULING

The Panel noted that in Case AUTH/2028/7/07 claims for '24-hour control' or '24-hour glycaemic control' for Lantus had been considered to not be capable of substantiation and exaggerated and misleading in that regard by the Appeal Board. Breaches of the Code were ruled.

In Case AUTH/2028/7/07 the data submitted in support of the claims had demonstrated the 24-hour duration of action of Lantus, not its efficacy in terms of glycaemic control. In the Appeal Board's view, control, in the context of diabetes, referred to glycaemic control ie the maintenance of blood glucose between set parameters. The Appeal Board noted that Lantus was a basal insulin designed to provide a background, constant suppression of blood glucose. In response to a question, Sanofi-Aventis had submitted that no type 1 diabetic would be controlled solely on Lantus and only about half of type 2 diabetics would be controlled on a combination of Lantus and oral agents. Most diabetics would thus not be 'controlled' with Lantus and would require short-acting insulin to cope with post prandial glucose peaks.

The Panel noted that the claim now at issue was '24-hour efficacy'. In the Panel's view the claim would be read by prescribers in the context of a basal insulin. Prescribers would take it to mean that Lantus provided a constant suppression of blood glucose over 24-hours ie that it had a 24-hour duration of action.

The Panel noted that the claim 'once daily – provides 24-hour efficacy' appeared in two leavepieces (LAN08/1037 and LAN08/1038) immediately under the prominent headline 'Lantus – control without compromise for your diabetes patients'. In that context the Panel considered that '24-hour efficacy' implied '24-hour control' and was thus in breach of the undertaking given in Case AUTH/2028/7/07. A breach of Clause 25 was ruled which was appealed.

The Panel considered that an undertaking was an important document. It included an assurance that that all possible steps would be taken to avoid similar breaches of the Code in future. It was very important for the reputation of the industry that companies complied with undertakings. In breaching its undertaking the Panel considered that Sanofi-Aventis had not maintained high standards and had brought discredit upon, and reduced confidence in the industry. Breaches of Clauses 9.1 and 2 of the Code were ruled which were appealed.

In the leavepiece LAN07/1333, '24-hour efficacy' was used as part of the Lantus product logo. Although page 2 of the leavepiece included the claim 'Lantus can enable people to improve their glycaemic control', the Panel did not consider that in the context in which it appeared, '24-hour efficacy' implied '24-hour control' as in the leavepieces considered above. In leavepiece LAN08/1039 the claim 'once daily – provides 24-hour efficacy' appeared beneath the claim 'Lantus – established efficacy ….' and in the mailer the claim '24-hour efficacy' appeared as a headline claim above data relating to duration of action. The Panel noted its comments above regarding a prescriber's expectation of Lantus and the view that would be taken of the claim '24-hour efficacy' in the context of a basal insulin. The Panel considered that there was data to show that Lantus had a 24-hour duration of action; section 5.1 of the SPC included a graph which showed that the activity profile of Lantus was smooth, peakless and almost constant between 9 and 24-hours in type 1 diabetics. The Panel considered that in the context in which it appeared in LAN07/1333, LAN08/1039

and LAN08/1041, the claim '24-hour efficacy' could be substantiated and no breach of Clause 7.4 was ruled. This ruling was not appealed.

The Panel noted that the leavepiece LAN08/1039 and the mailing LAN08/1041 both featured a graph depicting plasma glucose levels over time with Lantus and Levemir (Porcellati 2007b). The graph was drawn using results generated after two weeks of treatment and showed that in type 1 diabetics Lantus suppressed plasma glucose for 24-hour post injection whereas blood glucose levels started to rise in the Levemir group 15 hours post dose.

The Panel noted that Klein *et al* had measured the duration of action of Lantus and Levemir in type 2 diabetes and thus these results were not relevant to the graph at issue which detailed results in type 1 diabetes. Plank *et al* investigated the duration of action for five doses of Levemir (0.1, 0.2, 0.4 0.8 and 1.6U/kg) in type 1 diabetes. The results showed that the duration of action was dose dependent with doses of 0.8 and 1.6U/kg sufficient to maintain glucose levels for most subjects throughout a 24-hour period. The 0.4U/kg dose had a duration of action of 19.9 (± 3.2) hours). Heise and Pieber reviewed the pharmacodynamic data for Lantus and Levemir as derived from the glucose clamp technique. A common definition for duration of action (time from injection to plasma glucose >8.3mmol/l) was applied and study data were recalculated as necessary. The authors reported that the mean duration of action with both analogues was dose dependent, but in the clinically relevant range of 0.35-0.8U/kg it was close to 24-hours for both in type 1 diabetes. Heise and Pieber considered an abstract by Porcellati *et al* (2006) to be an outlier as it reported a shorter duration of action for Levemir (17.5 hours) than other authors. The Panel assumed that the abstract referred to was the forerunner of the full paper (Porcellati *et al* 2007b) from which the graph at issue was taken.

The Panel noted the comments of Heise and Pieber and considered that the graph at issue did not represent the balance of evidence with regard to the duration of action of Levemir in type 1 diabetes. Furthermore, the graph implied a duration of action of only 15 hours ie when plasma glucose levels began to rise whereas the authors themselves reported the duration of action to be 17.5 hours. The graph did not include a threshold blood glucose level beyond which the insulin could be regarded as no longer acting. The Panel considered that the graph was misleading and a breach of Clause 7.2 was ruled. The Panel further considered that the graph disparaged Levemir and a breach of Clause 8.1 was ruled. These rulings were appealed.

Although noting its rulings above the Panel did not consider that high standards had not been maintained. No breach of Clause 9.1 was ruled. This ruling was not appealed.

APPEAL BY SANOFI-AVENTIS

Sanofi-Aventis submitted that this complaint followed Case AUTH/2028/7/07, in which Novo Nordisk complained that the claims '24-hour control' and '24-hour glycaemic control' relating to Lantus were not capable of substantiation, arguing that a 24-hour duration of action had not been demonstrated. In its defence of these claims, Sanofi-Aventis provided information from three isoglycaemic clamp studies which demonstrated that Lantus exerted a duration of action of at least 24 hours (Lepore *et al*, Porcellati *et al*, 2007a and Porcellati *et al* 2007b). The Panel and the Appeal Board both agreed that the data provided supported the claim that Lantus had a 24-hour duration of action.

Although Lantus demonstrated a 24-hour duration of action, the Appeal Board recognised that its efficacy as a basal insulin was primarily the control of background or basal blood glucose levels (ie in the fasted intervals between meals), and that a proportion of patients required additional mealtime insulin doses to fully control their diabetes. All parties agreed that this observation was important and that as Lantus alone was unable to provide full 'glycaemic control' in all patients, the claims '24-hour control' and '24-hour glycaemic control' were therefore incapable of substantiation, despite the 24-hour duration of action as a background, basal insulin.

In response to this ruling, that 'a once daily dosage or a 24-hour course of action for a basal insulin did not equate to 24-hour glycaemic control', Sanofi-Aventis immediately withdrew the claim '24-hour control' from all materials and this wording had not been repeated in any subsequent item. This demonstrated the maintenance of high standards and fulfilment of all undertakings required as a consequence of this case.

In relation to the present complaint, Case AUTH 2141/7/08, Sanofi-Aventis submitted that having withdrawn '24-hour control', it sought to develop a claim to convey the 24-hour duration of action of Lantus that the Panel and Appeal Board recognised to exist, whilst avoiding the suggestion that Lantus alone was sufficient treatment for all patients with diabetes. The phrase '24-hour efficacy' was considered acceptable in this respect, given that efficacy was defined as 'the ability to produce a desired effect', and that the desired effect of a basal insulin such as Lantus was to provide constant suppression of background (non-meal-related) blood glucose levels. This wording was decided upon, taking directly into account the Appeal Board's observations.

Sanofi-Aventis was pleased that the Panel had decided it was clear that the claim '24-hour efficacy' would be read by prescribers in the context of a basal insulin, and that prescribers would take it to mean that Lantus provided a constant suppression of blood glucose over 24 hours, ie that it had a 24-

hour duration of action. This was exactly the intent of Sanofi-Aventis in making this claim, and it was pleased that the Panel considered the claim in itself met these requirements, and was not in breach of the Code (as demonstrated by the ruling of 'no breach' made in respect of every use of the claim bar two).

In relation to items LAN 08/1037 and LAN 08/1038 Sanofi-Aventis appealed the Panel's rulings of breaches of Clauses 2, 9.1 and 25. Sanofi-Aventis disagreed that the use of the claim '24-hour efficacy' in these two items implied glycaemic control. In considering its understanding of this claim in general, the Panel was clear in how this statement would be perceived: 'the claim would be read by prescribers in the context of a basal insulin. Prescribers would take it to mean that Lantus provided a constant suppression of blood glucose over 24 hours, ie that it had a 24-hour duration of action'.

Sanofi-Aventis submitted that this was a firm conclusion that indicated that the intended audience would be clear that the claim referred to the duration of efficacy of the product and not the ability of Lantus to achieve glycaemic control in all patients – the finding in Case AUTH/2028/7/08. Furthermore, this conclusion was matched by the Appeal Board's conclusion in Case AUTH/2028/7/08, which implied that 24-hour effect and glycaemic control could not be considered the same: 'a once daily dosage or a 24-hour course of action for a basal insulin did not equate to 24-hour glycaemic control'.

Sanofi-Aventis therefore submitted that the statement '24-hour efficacy', as used in these two items, still had the primary meaning that Lantus had a 24-hour period of efficacy as a basal insulin, and did not suggest that it could of itself achieve full glycaemic control in all diabetics.

The Panel stated that it was the context in which this statement was made that had resulted in the finding of a breach of Clause 25. The concern of the Panel was that in the item, the claim (although made as a stand-alone statement with the primary intent above) would be interpreted as implying 24-hour control, as it appeared below the headline 'Lantus – control without compromise for your diabetes patients'.

Whilst agreeing that it was appropriate to look at the statement 'in context', Sanofi-Aventis submitted that the context should not be limited to this headline alone, but that the item must be viewed in its entirety. The breach ruled in Case AUTH/2028/7/07 was that '24-hour control' implied that Lantus alone could achieve glycaemic control for all patients with diabetes. In both of these pieces, for which a breach had been ruled, it was made clear that once Lantus had been titrated to an effective dose, it was then appropriate to consider the addition of rapid acting insulin. Therefore, when viewed in the context of the entire item, Sanofi-Aventis disagreed that these promotional items sought to promote Lantus as an agent that, when used in isolation, could provide effective glycaemic control in all patients – the need for additional insulin was clearly recognised and overtly stated in both. In conclusion, Sanofi-Aventis considered that these two items had been developed taking fully into account the findings from Case AUTH/2028/7/07:

- The claim '24-hour efficacy' was agreed to reflect the duration of action of Lantus.
- It was not claimed that Lantus could provide glycaemic control in isolation – the need for additional rapid acting insulin was overtly stated.

Sanofi-Aventis therefore considered that the undertaking in Case AUTH/2028/7/07 had been met, that items LAN 08/1037 and LAN 08/1038 complied with the Code and that high standards had been maintained throughout.

In relation to items LAN 08/1039 and LAN 08/1041 in which the Panel ruled a breach of Clauses 7.2 and 8.1 Sanofi-Aventis noted that both contained a graph, reproduced without amendment (other than extending the suppressed scales back to zero) from Porcellati *et al* 2007b.

The Panel considered that the graph, although accurately representing the 24-hour duration of action of Lantus in patients with type 2 diabetes, misled as to the duration of action of Levemir. The Panel appeared to have formed an opinion that a duration of action of close to 24 hours existed for Levemir in patients with type 1 diabetes, and that this study, being substantially shorter, misled through being inconsistent with the wider body of evidence. Sanofi-Aventis submitted that this position was not an accurate assessment of the existing body of evidence, and therefore it appealed both breaches of the Code in respect to these two items.

Firstly, the Panel had disregarded Klein *et al* on the basis that it was in patients with type 2 diabetes, irrelevant to the graph at issue. Sanofi-Aventis agreed with the Panel in this respect.

The Panel next considered Plank *et al*, which examined the duration of action of Levemir at a range of doses from 0.1 to 1.6U/kg. The Panel noted that doses of 0.8 and 1.6U/kg were sufficient to maintain glucose levels for most subjects throughout 24 hours. These doses were considerably greater however than the dose used by Porcellati *et al* (2007b) (0.35U/kg). The Panel had also not taken into account how these doses (tested in a phase 1 dose proportionality study) related to the dose usually found in clinical practice. Plank *et al* made no comment on how these doses related to clinical practice; however, the EPAR for Levemir indicated that in all studies of patients with type 1 diabetes the dose of Levemir ('basal') had a range of only 0.27 to 0.49U/kg:

Taking this into consideration, Sanofi-Aventis

submitted that it was clear that although in this pharmacokinetic study Levemir might have a duration of action of close to 24 hours at supra-therapeutic levels of 0.8 and 1.6U/kg, at the range encountered in usual care (0.27 to 0.49U/kg) the duration of action was less (12.1 hours for 0.2U/kg; 19.9 hours at 0.4U/kg). These findings were consistent with Porcellati *et al* (2007b), especially when it was considered that the latter used a normal clinical dose of 0.35U/kg of Levemir. Sanofi-Aventis therefore considered that the data in Porcellati *et al* (2007b) was consistent with that demonstrated by Plank *et al*.

Next, the Panel considered the review by Heise and Pieber, and focused on the statement that 'the mean duration of action of both analogues was dose dependent, but in the clinically relevant range of 0.35 - 0.8 units/kg it was close to 24 hours'. Sanofi-Aventis was again concerned about the Panel's interpretation of this statement. Firstly, this review only contained three studies of Levemir in type 1 diabetes in which a duration of action was given:

- Plank *et al*, in which the duration of action of Levemir at clinical doses of 0.2 - 0.4U/kg was approximately 12.1 - 19.9 hours.
- Heise *et al* (2004) demonstrated a duration of action of action of 23 hours at a clinical dose of 0.4U/kg.
- Porcellati *et al* (2007b) demonstrated a duration of action of 17.5 hours at a dose of 0.35U/kg.

The Panel highlighted the authors' statement that the last study, by Porcellati, should be disregarded as an outlier simply because the values were lower than those in the other studies. In stating this, the authors had, however, failed to provide any quality assessment of the study or rational, evidence-based reason for disregarding the statement.

Taking into account the similar results from Plank *et al* (dose for dose), Porcellati *et al* (2007b) should be considered as replicating the findings, not falling as an outlier, and the authors' statements appeared to have misled the Panel. Far from failing to represent the body of evidence for the duration of action of Levemir in type 1 diabetes, Porcellati *et al* (2007b) and Plank *et al* demonstrated similar durations of action for Levemir and between them represented the bulk of the evidence (two out of three clamp studies in this review for which a duration of action of Levemir was stated).

In addition to this, the Levemir SPC quoted further durations of actions of Levemir in patients with type 1 diabetes ie 12, 17 and 20 hours at doses of 0.2, 0.3 and 0.4 U/kg respectively (presumably derived from Plank *et al*), representing the doses expected in clinical practice, not the supra-therapeutic 0.8 - 1.6U/kg doses focussed on by Heise and Pieber which appeared to have dominated the Panel's conclusions.

In summary, Sanofi-Aventis disagreed with the Panel's conclusion that Porcellati *et al* (2007b) did not represent the balance of evidence with regard to Levemir's duration of action; when similar doses were considered – doses that would be used in clinical practice – the Porcellati data were entirely consistent with, and formed a substantial component of, this body of evidence. As such, Sanofi-Aventis considered use of this data was not misleading nor disparaging, the latter particularly in view of the fact that the Porcellati data were also consistent with the 12-20 hour duration of action of Levemir in type 1 diabetes quoted in the Levemir SPC. Sanofi-Aventis considered that high standards had been maintained throughout and that no breach of the Code had occurred.

COMMENTS FROM NOVO NORDISK

Novo Nordisk upheld all its arguments detailed in its complaint and agreed with the Panel that the claim '24 hour efficacy' tried to communicate the same product message (namely '24-hour control') which had been ruled to be misleading by the Appeal Board (Case AUTH/2028/7/07). Thus it had breached Clauses 25, 9.1 and 2 of the Code.

Furthermore Novo Nordisk noted that if Sanofi-Aventis' definition of 'efficacy' ('the ability to produce a desired effect') was accepted then Lantus would be expected to provide normoglycaemic or near normoglycaemic blood glucose values in terms of fasting and pre-meal blood glucose levels. However, as it was discussed and agreed in Case AUTH/2028/7/07, Lantus itself could not provide these values (especially in the case of pre-lunch and pre-dinner blood glucose levels), in all cases of type 1 and in a significant proportion of type 2 diabetes, without combining it with a soluble insulin preparation in a clinical setting.

Although Novo Nordisk agreed with Sanofi-Aventis that the item must be viewed in its entirety, it strongly disagreed that the bullet-point about adding rapid acting insulin would eliminate the implication of the claim that Lantus could provide glycaemic control in isolation. In fact the bullet-point in question actually recommended adding rapid acting insulin to avoid weight gain, with a higher basal insulin dose (in case of further titration), and *did* not highlight the limitation of Lantus therapy in achieving appropriate blood glucose control without post prandial cover. Therefore Novo Nordisk still alleged that Sanofi-Aventis was trying to imply the same message with the claim of '24-hour efficacy' in context with the claim of 'Once daily' (as it appeared on the back page of each item), as it had implied with the claim of '24-hour control'.

With regard to using the graph from the Porcellati *et al* (2007b), Novo Nordisk agreed with the Panel's ruling. With regard to the appeal Novo Nordisk did not agree with Sanofi-Aventis (or with the Panel) that Klein *et al* would be irrelevant to the graph at issue. Since promotional materials should be balanced, fair and consider all the available medical

evidence, Klein *et al* could not be omitted in materials dealing with both types of diabetes (LAN 08/1039). It should be considered as an even more important source of scientific information in the case of the other promotional item (LAN 08/1041) which focused solely on type 2 diabetes. In fact from this perspective, the result from Porcellati *et al* (2007b), conducted solely in type 1 diabetic patients, could be regarded as irrelevant.

Novo Nordisk noted that Sanofi-Aventis consistently suggested that Plank *et al* confirmed the results of Porcellati *et al* (2007b). In fact the closest comparable dose in Plank *et al* to that used in the clamp study by Porcellati *et al*, (2007b) (0.35U/kg) was 0.4U/kg. At this dose the duration of action for Levemir was revealed as 19.9±3.2 hours which was considerably longer than that suggested by the graph from Porcellati *et al* (2007b).

Sanofi-Aventis criticised the Panel's interpretation of a conclusion from the comprehensive clamp review paper published by Heise and Pieber. The Panel noted the limitation of the review that only three clamp studies with Levemir in type 1 diabetes were analyzed. However there were four trials with Lantus which the authors considered on the basis of pre-defined criteria. Novo Nordisk submitted that this kind of difference would not make the conclusions from the Levemir studies irrelevant. Furthermore a recent clamp trial comparing Lantus and Levemir in type 1 diabetes (Bock *et al* 2008) revealed completely different results to Porcellati *et al*, (2007b). In fact Bock *et al* confirmed the conclusion of Heise and Pieber, in that the durations of action of Levemir and Lantus were comparable over a 24-hour period which made them suitable for once-daily dosing in most subjects (23.3±4.9 hrs and 27.1±7.7 hrs respectively at steady state). Novo Nordisk alleged that the evidence from these clamp studies which suggested similar durations of action for Lantus and Levemir were reassuring and further confirmed the conclusion by Heise and Pieber that Porcellati *et al*, (2007b) should be considered as an outlier. Novo Nordisk also noted again the contradiction between the results from the clinical part and the clamp part of Porcellati *et al* (2007b). Sanofi-Aventis had only referred to the results from the clamp part of this study in its promotional materials, and had hidden the inconsistent results from the clinical part.

APPEAL BOARD RULING

The Appeal Board noted that in Case AUTH/2028/7/07 claims for '24-hour control' or '24-hour glycaemic control' for Lantus had been considered to not be capable of substantiation and exaggerated and misleading. Breaches of the Code were ruled.

Turning to the case now before it the Appeal Board noted that the intended audience for the two leavepieces (LAN08/1037 and LAN08/1038) were diabetes nurse specialists, diabetologists and GPs with an interest in diabetes. The Appeal Board considered that although the claim 'Once-daily – provides 24-hour efficacy' appeared below the claims 'Lantus-control without compromise for your diabetes patients', given the audience it would not be taken to imply '24-hour-control' but a claim for duration of action. The Appeal Board had some concerns about the claim and its context but on balance decided that Sanofi-Aventis had not breached its undertaking given in Case AUTH/2028/7/07. The Appeal Board ruled no breach of Clause 25 and consequently no breach of Clauses 9.1 and 2. The appeal on this point was thus successful.

The Appeal Board noted that the leavepiece LAN08/1039 and the mailer LAN08/1041 both featured a graph depicting plasma glucose levels over time with Lantus and Levemir (Porcellati 2007b). The graph was drawn using results generated after two weeks of treatment and showed that in type 1 diabetics Lantus constantly suppressed plasma glucose over a 24-hour period post dose whereas blood glucose levels started to rise in the Levemir group after 15 hours.

The Appeal Board considered that the results were not inconsistent with the products' SPCs. Lantus should be administered once daily. The recommended initiation of Levemir in combination with oral antidiabetic agents was once daily. When Levemir was used as part of a basal-bolus regimen it should be administered once or twice daily based on individual patient needs. The Appeal Board noted that the balance of evidence showed that Lantus suppressed plasma glucose for a longer period of time than Levemir.

The Appeal Board did not consider that the graph was either misleading or that it disparaged Levemir. No breach of Clauses 7.2 and 8.1 were ruled. The appeal on these points was successful.

2 Claim 'In clinical practice, after switching from other treatments, Lantus is associated with a lower risk of hypoglycaemia compared to insulin detemir'

Novo Nordisk noted that this claim appeared in one of the leavepieces (LAN08/1038) and in the mailer (LAN08/1041).

COMPLAINT

Novo Nordisk noted that the claim was substantiated by findings from a retrospective GP database analysis (Currie *et al* 2007). The authors compared the reported hypoglycaemic event rate prior to and following initiation of basal Lantus and Levemir (a secondary endpoint of the analysis) and concluded that the risk reduction in hypoglycaemia was significantly greater with Lantus. However, there were some limitations of this analysis which needed to be considered to decide whether the

claim, substantiated by this paper, was misleading or not. The authors compared the clinical outcomes of 5,683 Lantus patients with outcomes of only 694 patients using Levemir. The huge difference in patient numbers obviously reflected the more established clinical experience of using Lantus at that time, ie prescribers were more familiar with its use. Therefore the analysis was biased in favour of Lantus.

Although Currie *et al* analysed the primary endpoint of HbA1c change, and the secondary endpoint of weight change separately in type 1 and type 2 diabetes patients, they failed to follow this fair and highly relevant approach with regard to hypoglycaemia. Further, they failed to differentiate between major and minor hypoglycaemic episodes or episodes that occurred during the day or at night. This lack of clarification raised the question of whether this analysis provided clinicians with any useful findings regarding hypoglycaemia. Defining the types of hypoglycaemic events would be crucial in order to make clinically relevant conclusions from this analysis.

It was well know that hypoglycaemic risk was markedly different in type 1 and type 2 diabetes. The literature clearly differentiated between major and minor hypoglycaemic episodes. Whilst the major hypoglycaemic event rate was approximately 1 event/patient-year in type 1 diabetes (Cryer *et al*, 2007 and Zammitt and Frier 2005), in type 2 diabetes treated by insulin it was at least a third of that: 0.28 (Henderson *et al* 2003) to 0.35 (Donnelly *et al* 2005) events/patient-year. In case of minor events the typical event rate in type 1 diabetes was 104 events/patient-year (Cryer *et al* and Zammitt and Frier) whilst in type 2 diabetes it was approximately 16.5 events/patient-year (Abraira *et al* 1995 and Donnelly *et al*). There seemed to be agreement in the literature that there was a higher incidence of hypoglycaemic episodes in patients with a more advanced stage of type 2 diabetes ie those requiring more intensive antihyperglycaemic therapy (Cryer *et al* and Zammitt and Frier).

These differences in hypoglycaemic risk could be partially explained by the use of different insulin regimens. Whilst type 1 diabetics almost exclusively used a basal-bolus regimen, in type 2 diabetes basal insulins could be used as part of basal-oral or basal-bolus regimens. Since basal-bolus therapy was a much more aggressive approach to control blood glucose levels, and was usually applied at a considerably later (more severe) stage of type 2 diabetes, it was connected with a significantly higher hypoglycaemic event rate than a basal-oral regimen.

One might reasonably assume that in the case of type 1 diabetes, the only flaw in Currie *et al* was the above mentioned 'familiarity' effect in terms of Lantus, since both preparations were used as part of a basal-bolus regimen. However in type 2 diabetes it had to be presumed that apart from this effect there was at least one more bias in favour of Lantus. Whilst it was not clear from the published paper, it was reasonable to assume that many more patients in the Lantus group would have been treated with basal-oral treatment. In the Levemir group the vast majority of the patients would have been treated with a basal-bolus regimen. This was because Lantus had a licence for both basal-oral and basal-bolus use, whilst Levemir only had a licence for basal-bolus use during the analysed period.

Therefore to compare the hypoglycaemic rate reduction without taking into account the type of diabetes and the insulin regimen for those with type 2 diabetes was misleading. Further, it was disappointing that information on the use of bolus insulin, readily available from the THIN database, had been clearly overlooked. The authors simply chose to compare the hypoglycaemic risk reduction in the combined cohort of type 1 and type 2 patients and failed to make any distinction between basal-oral users and basal-bolus users in the type 2 cohort.

The claim at issue was purely based on the results from this flawed analysis. However relevant data from published randomized clinical trials (RCTs) provided a much higher level of evidence. These trials provided detailed results in terms of different types of hypoglycaemic events, relating to Levemir and Lantus when used as part of the same regimen. There were at least two direct, randomized comparisons of Lantus and Levemir (Pieber *et al* 2007 and Rosenstock *et al* 2008). The results from Pieber *et al*, which compared the two as part of basal-bolus therapy in type 1 diabetes, contradicted those of Currie *et al*. In Pieber *et al* Levemir was associated with a significantly lower risk of all nocturnal minor (RR=0.68 [0.46-0.99], p=0.045) and 24-hour major (RR=0.28 [0.08-0.98], p=0.047) hypoglycaemic events despite providing the same overall metabolic control (final HbA1c of 8.16% and 8.19% for Levemir and Lantus respectively, p=ns). Rosenstock *et al* compared Lantus and Levemir as part of basal-oral therapy in type 2 diabetes and was unable to detect any difference between the two in terms of any type of hypoglycaemic risk.

Novo Nordisk believed that Sanofi-Aventis had again cherry-picked the results from a retrospective database analysis, which was severely flawed in terms of hypoglycaemic risk analysis, to substantiate the claim. The company had clearly disregarded all the other published evidence which had revealed completely different results. Therefore the claim was inaccurate, unbalanced, unfair, and ambiguous, it was not based on an up-to-date evaluation of all available evidence and disparaged Levemir in breach of Clauses 7.2, 8.1 and 9.1 of the Code.

RESPONSE

Sanofi-Aventis noted that this complaint followed Case AUTH/2038/7/07 in which Novo Nordisk had alleged that the claim 'Lantus significantly reduced

hypoglycaemia over Levemir in both type 1 and type 2 diabetes', based on the retrospective observational study by Currie *et al*, was not capable of substantiation.

The argument presented by Novo Nordisk was that Currie *et al* was conducted in a pooled population of type 1 and type 2 diabetics, and that differing evidence from RCTs had been overlooked. Novo Nordisk cited Pieber *et al* and Rosenstock *et al* to illustrate the different findings between observational studies and RCTs.

This original statement was ruled in breach of the Code because the heading implied that both type 1 and type 2 patients would expect this benefit, and this could not be substantiated from the pooled analysis. To address the Panel's comments and rulings Sanofi-Aventis removed the final wording from the claim ('… in both type 1 and type 2 diabetes').

With respect to the assertion that the study was of a retrospective database analysis, and did not take into account different findings observed in RCTs, the Panel ruled that there were important differences between observational studies and RCTs, and that it was appropriate to report the data of observational studies. The Panel also considered that the origin of the data was clear to readers. No breach was ruled in this respect.

In the complaint now at issue, Novo Nordisk had once again alleged that use of Currie *et al* to support the claim 'In clinical practice, after switching from other treatments, Lantus is associated with a lower risk of hypoglycaemia compared with insulin detemir' was inappropriate because:

- Firstly, that the authors' analysis was flawed – having been performed on a pooled cohort as opposed to separate cohorts for patients with type 1 and type 2 diabetes.

Whilst Sanofi-Aventis agreed that although this might have been desirable, the analysis performed would have been limited by the nature of information recorded in GP systems. In almost all cases differentiation between severe/mild, nocturnal/daytime hypoglycaemia would not be possible as there was only a single Read code for hypoglycaemia, preventing such sub-classification.

Nonetheless, although the published paper might be open to some critique, it had been published and peer reviewed and was a robust analysis of the rates of hypoglycaemia associated with the use of the two insulins as observed in everyday clinical practice. The hypoglycaemia claim in question was a straightforward representation of this published data. Challenge of the content of the article should be addressed to the journal, not through the Authority.

In conclusion, Novo Nordisk considered that different use of the two insulins might have been responsible for a difference in the observed hypoglycaemia rates. This point had already been considered and dismissed in the initial case; the Panel concluded that the Levemir SPC referred to use with oral hypoglycaemic agents at the time the analysis was performed, and that therefore the difference in usage suggested by Novo Nordisk could not simply be assumed to have occurred.

- Secondly, Novo Nordisk was again concerned that the use of Currie *et al* to support this claim overlooked RCT data, Pieber *et al* and Rosenstock *et al* as put forward in Case AUTH/2038/7/07 and ruled not to be in breach of the Code.

With respect to this assertion, Sanofi-Aventis' response was the same as that provided in the original case. To summarise, this was that: whilst RCT data was fundamental to the evaluation of any new product, a range of data sources were collectively crucial in determining the impact of any given therapy in real life, including observational data; RCTs had their own limitations, in particular being performed on a highly selected cohort of patients which reduced the ability to generalise results to real life practice and a large observational study such as Currie *et al* was much more generalisable to the population than a small RCT, and a good quality observational study was rated level 2b in standard evidence based medicine hierarchies, the same level as a poor quality RCT.

In considering Case AUTH/2038/8/07 the Panel recognised that there were important differences between observational studies and RCTs, and that it was appropriate to report the data of observational studies. In recognition of this, Sanofi-Aventis continued use Currie *et al* to support the claim now in question.

With respect to the current allegation made by Novo Nordisk, Sanofi-Aventis disagreed with the assertion that the claim continued to be made contrary to it being an up-to-date evaluation of all the evidence available. Currie *et al* remained a robust report of a large scale observational study of the effectiveness of the two insulins when used in normal clinical practice, and it was important for physicians to know about it. Novo Nordisk did not appear to have advanced its argument beyond that considered in Case AUTH/2038/8/07, and Sanofi-Aventis was disappointed to have to restate the same response to the same allegations made a year ago. As opposed to cherry-picking, this appeared to be a second bite at the cherry, the opportunity for Novo Nordisk to appeal the original finding was declined.

- Finally, Sanofi-Aventis re-iterated that the claim had already been voluntarily withdrawn as a result of inter-company dialogue (on 18 June 2008).

Although Sanofi-Aventis steadfastly defended the right to publicise the comparative rates of

hypoglycaemia seen in Currie *et al*, it recognised that the phrase 'In clinical practice', although intended to convey that this data was from an observational study, might not be perceived as such by all readers. This claim had therefore been discontinued in this form and all materials in which it was contained had been withdrawn.

In summary, Sanofi-Aventis was confident that the items quoted by Novo Nordisk had been produced taking into account the requirements of the Code and the findings in Cases AUTH/2028/7/07 and AUTH/2038/8/07. All breaches ruled in these two cases had been acted upon and the items amended accordingly.

Sanofi-Aventis denied that it had breached its undertaking and also with Novo Nordisk's other assertions, most of which appeared to be a restatement of complaints which the Panel found to be unproven when first considered. Sanofi-Aventis considered that all actions had been in accordance with the requirements of the Code, and that high standards had been maintained throughout.

Finally, Sanofi-Aventis was disappointed that concerns regarding a claim which it considered had been resolved through inter-company dialogue had regardless been referred for consideration by the Authority.

PANEL RULING

The Director noted Sanofi-Aventis' submission that in its view inter-company dialogue regarding the claim at issue had been successful. Sanofi-Aventis had agreed to withdraw all materials which featured the claim 'In clinical practice, after switching from other treatments, Lantus is associated with a significantly lower risk of hypoglycaemia compared with insulin detemir ($p<0.05$)' only in as much as the phrase 'In clinical practice' did not convey the fact that the data was from a retrospective database analysis. It appeared that in all other respects Sanofi-Aventis intended to continue using the claim. The Director thus considered that inter-company dialogue had not been successful and so the matter was referred to the Panel for it to consider the claim minus the phase 'In clinical practice'.

The Panel noted that the leavepiece (LAN08/1038) was specifically about the use of Lantus in type 2 diabetics. The final page featured the claim at issue referenced to Currie *et al* a study which had demonstrated that in a pooled cohort of type 1 and type 2 diabetics, patients switched to Lantus had a lower relative risk of hypoglycaemia than those switched to Levemir. Given the specificity of the leavepiece, however, the Panel considered that a claim based on pooled data from type 1 and type 2 diabetics was misleading. A breach of Clause 7.2 was ruled which was appealed. The Panel did not consider that the claim disparaged Levemir and so no breach of Clause 8.1 was ruled. The Panel noted that use of Currie *et al* and the need to ensure that readers understood that the hypoglycaemia data was from a pooled cohort of patients had been at issue in Case AUTH/2038/8/07. The Panel considered that to again use the pooled data in a way that was misleading meant that high standards had not been maintained. A breach of Clause 9.1 was ruled which was appealed.

The mailing (LAN08/1041), 'Why choose Lantus' was not specific as to the type of diabetic patients at issue – the mailing referred to both type 1 and type 2 patients. As in the leavepiece above the claim at issue had been derived from Currie *et al*. The Panel noted that the data was generated when the licence for Levemir did not include management of type 2 diabetes except as part of a basal-bolus regimen. Levemir could now be used as part of a basal-oral regimen and so patients who were less prone to hypoglycaemic attacks could be treated. The pooled cohort of type 1 and type 2 diabetics included in Currie *et al* was thus likely to be different to the mixed group of diabetics that a prescriber might now treat with either Lantus or Levemir and so on that basis the Panel considered that the claim at issue was misleading. A breach of Clause 7.2 was ruled which was appealed. Although noting this ruling the Panel did not consider that high standards had not been maintained. No breach of Clause 9.1 was ruled. The Panel did not consider that the claim disparaged Levemir. No breach of Clause 8.1 was ruled.

APPEAL BY SANOFI-AVENTIS

Sanofi-Aventis noted that this complaint followed Case AUTH/2038/7/07, in which Novo Nordisk complained that the statement 'Lantus significantly reduced hypoglycaemia over Levemir in both type 1 and type 2 diabetes', based on a retrospective observational study by Currie *et al*, was not capable of substantiation. Novo Nordisk had argued that Currie *et al* was conducted in a pooled population of type 1 and type 2 diabetics, and that the claim overlooked differing evidence from RCTs. Pieber *et al* 2007 and Rosenstock *et al* were cited by Novo Nordisk to illustrate the different findings between observational studies and RCTs.

With respect to the assertion that Currie *et al* was of retrospective database analysis and did not take into account different findings observed in RCTs, the Panel ruled (in Case AUTH/2038/7/07) that there were important differences between observational studies and RCTs, and that it was appropriate to report the data of observational studies. The Panel also considered that the origin of the data was clear to the reader. No breach was ruled in this respect, and Sanofi-Aventis therefore considered it appropriate to continue to utilise this data, provided that it was made clear that the study was observational (reflecting clinical practice) rather than from an RCT.

The breach of the Code that was found with respect to this claim arose from the heading implying that

both type 1 and type 2 patients would expect this benefit, whereas this could not be substantiated from the pooled analysis (despite the author's conclusion that 'Treatment with insulin glargine in both type 1 and type 2 diabetes resulted in … a reduction in hypoglycaemia when compared to treatment with insulin detemir').

In response to this ruling Sanofi-Aventis removed '… in both type 1 and type 2 diabetes' from the claim. The Panel's finding was that benefits had been claimed separately in patients with type 1 and type 2 diabetes, and this could not be supported by the pooled analysis in which no such differentiation had been made – only an overall benefit in the total cohort of patients had been demonstrated. Sanofi-Aventis considered that removing the specific references to individual patient types had made the claim consistent with the pooled analysis from the supporting reference.

Sanofi-Aventis noted that in the present complaint, Case AUTH/2141/7/08, Novo Nordisk had once again alleged that use of Currie *et al* to support this claim was inappropriate because the analysis performed by the authors was methodologically flawed as the use of the products might have been different in clinical practice than in RCTs. Specifically, that a difference in the SPCs of the two insulins might have been responsible for a difference in the observed hypoglycaemia rates. Further, that using Currie *et al* to support the claim again overlooked RCT data (quoting only the same studies Pieber *et al* and Rosenstock *et al* as quoted in Case AUTH/2038/7/07 – ruled then not to be in breach of the Code).

Sanofi-Aventis was disappointed that Novo Nordisk had ignored the voluntary undertaking and withdrawal of these items, as agreed through inter-company dialogue – this seemed contrary at least to the spirit of the Code. Sanofi-Aventis was also disappointed that despite the ruling in Case AUTH/2038/7/07 (in which the Panel recognised that there were important differences between observational studies and RCTs, and that it was appropriate to report the data of observational studies), Novo Nordisk had raised the same objection using the same argument as in this case (which resulted in a finding of no breach). Sanofi-Aventis was similarly disappointed that, as a result of this unwarranted complaint, the Panel had reversed its earlier decision without any additional evidence presented by Novo Nordisk to advance its argument other than that proposed in support of its initial case. Sanofi-Aventis was also concerned that the Panel had been directed to consider how Sanofi-Aventis might use a claim in the future, rather than making a judgement on the use that had occurred. Sanofi-Aventis therefore appealed the Panel's rulings of breaches of the Code.

Sanofi-Aventis noted the Panel's rulings of a breach of Clauses 7.2 and 9.1 in relation to LAN08/1038 and submitted that the Panel had considered that this leavepiece was specifically about type 2 diabetes, and had ruled that to include information on hypoglycaemia in a pooled group of patients with both types of diabetes was therefore misleading. However, the leavepiece did not specifically discuss type 2 diabetes, but discussed use of Lantus in combination with oral hypoglycaemic agents. There was no 'Type 2 Diabetes' title to the document (as opposed to that found in LAN 07/1333 for example), and although the majority of oral hypoglycaemic agents were used in type 2 diabetes, there was still some use, low but significant nonetheless, in type 1 diabetics who were obese and had an element of insulin resistance in addition to their insulin deficiency (so called 'double diabetes') (Moon *et al* 2007).

Sanofi-Aventis therefore submitted that this 'Oral Hypoglycaemic Agent' (not 'Type 2 Diabetes') leavepiece could be considered relevant to both type 1 and type 2 diabetes, and that the Panel's decision that it was limited to type 2 diabetes had resulted in the ruling that the use of data from type 1 and type 2 patients was misleading and not in keeping with high standards. As the leavepiece was not restricted solely to type 2 diabetes, Sanofi-Aventis considered that it was appropriate to include data on patients with diabetes as a whole, and that the leavepiece was not misleading, and that high standards had been maintained.

Sanofi-Aventis noted the Panel's rulings of a breach of Clause 7.2 in relation to item LAN08/1041 and submitted that it was concerned that the Panel, in making this ruling, had reversed its findings in Case AUTH/2038/7/07, without any additional substantive evidence having been demonstrated by Novo Nordisk.

Having defended exactly the same allegation in Case AUTH/2038/7/07, Sanofi-Aventis had continued to use this information regarding rates of hypoglycaemia in clinical practice in the belief that it continued to meet the requirements of the Code. If Novo Nordisk considered that this was not so then it should have appealed the initial ruling – to simply repeat the argument in a new complaint in the hope of a different ruling appeared unjust and set a dangerous precedent. Sanofi-Aventis therefore appealed this finding.

The Panel had reached the opinion that that different patterns of use of the two insulins might have been responsible for a difference in the observed hypoglycaemia rates demonstrated in Currie *et al*, in particular that in type 2 diabetes use in the absence of oral hypoglycaemic agents might have been favoured. This point was considered in Case AUTH/2038/7/07 and dismissed, the Panel concluded that the absence of a specific indication for use with oral hypoglycaemic agents would not prevent this occurring in clinical practice, given that this was the usual pattern of care in type 2 diabetes and especially as the Levemir SPC referred to use with oral hypoglycaemic agents when the analysis was performed. The difference in usage suggested

by Novo Nordisk could not simply be assumed to have occurred.

In reiterating this same argument, again no evidence had been put forward that demonstrated in patients with type 2 diabetes a different pattern of use when the study was performed compared with current practice; Novo Nordisk had only suggested that this might have been the case. In fact, Novo Nordisk highlighted that the overall rate of hypoglycaemia was approximately three times higher in type 1 diabetics than type 2 diabetics – as there were equal numbers of each in the study any impact from different use in patients with type 2 diabetes might therefore be considered small with respect to the overall results demonstrated, and unlikely to significantly alter the conclusion. Not withstanding this point, although the published paper might be open to some critique, it had been published and peer reviewed and it represented a robust demonstration of the effects of using each of the two insulins in clinical practice rather than in RCTs.

In summary, Sanofi-Aventis submitted that in the absence of any new evidence to suggest otherwise, this claim remained robust and its use did not mislead, rather it provided valuable information on the outcomes seen when Levemir and Lantus were used in clinical practice as opposed to within clinical trials, and that the item met the requirements of the Code. The claims in question were capable of substantiation.

COMMENTS FROM NOVO NORDISK

Novo Nordisk noted Sanofi-Aventis' disappointment that it had ignored the voluntary undertaking and withdrawal of all items that included the claim 'In clinical practice, after switching from other treatments, Lantus is associated with a lower risk of hypoglycaemia compared to insulin detemir'. However the undertaking Sanofi-Aventis agreed in the inter-company dialogue related to the current format of the claim. As Sanofi-Aventis had emphasised the part of the claim 'In clinical practice' was not sufficiently clear in communicating that the results came from a retrospective database analysis (Currie *et al*), Sanofi-Aventis also noted that the claim was used in a 'one-off' mailer. However, this was not the only 'one-off' mailer in which Sanofi-Aventis had used this claim. This was the second 'one-off' mailer to use the same claim with minor changes. Sanofi-Aventis' clear message was that Lantus was associated with significantly fewer hypoglycaemic events than Levemir which Novo Nordisk considered to be seriously misleading, particularly given the results coming from head-to-head comparisons in RCTs between the two compounds and the flaws in the substantiating analysis. Given that Sanofi-Aventis slightly modified the wording of the claim without actually changing its essence and meaning, Novo Nordisk was seriously worried about further future promotional materials that portrayed the same claim (ie that Lantus was better than Levemir with regard to hypoglycaemic risk). For these reasons Novo Nordisk considered that Sanofi-Aventis' undertaking offered in the inter-company dialogue was wholly inadequate.

Sanofi-Aventis' appeal suggested that the promotional item LAN 08/1038 did not specifically discuss type 2 diabetes. Since it focused on the use of Lantus in combination with oral antidiabetics it could be relevant to both type 1 and type 2 diabetes. However, no oral antidiabetic medicine was licensed for use in combination with insulin therapy in type 1 diabetes. In fact all the currently available oral agents indicated in Section of 4.1 of their respective SPCs that they could be used in type 2 diabetes not type 1 diabetes. Any use of these medicines in type 1 diabetes would be outside the licence. Sanofi-Aventis' argument was therefore completely irrelevant. Although a limited number of scientific papers had investigated the use of oral antidiabetic medicines in type 1 diabetes, the evidence was so limited that there was no guideline recommending such use (NICE Type 1 diabetes in adults: national clinical guideline for diagnosis and management, 2004). It was inevitable that readers would consider this material was only relevant to type 2 diabetes.

Lastly Novo Nordisk turned to the argument relating to the difference in the product licences and potential impact on the hypoglycaemic results. Sanofi-Aventis noted that when the analysis was conducted by Currie *et al*, there was no difference between the licences and suggested that it could not be considered as a flaw of the study; this was incorrect. The period analysed and not the time of the analysis, covered the years 2004-2006. Levemir was not approved for use in combination with oral antidiabetics until March 2007 – Currie *et al* was published in February 2007! This meant that the difference in their licences would have significant impact on the hypoglycaemia results, as discussed in detail above.

On the basis of the above Novo Nordisk agreed with the Panel's decisions and upheld its complaints regarding the materials which were the subject of the appeal by Sanofi-Aventis.

APPEAL BOARD RULING

The Appeal Board did not accept Sanofi-Aventis' submission that Novo Nordisk's allegations were the same in Case AUTH/2038/7/07 as in the case currently under consideration. The Panel had considered that in Case AUTH/2038/7/07 it was sufficiently clear that the data was from an observational study (Currie *et al*). Further the Panel did not consider that, on the basis of the two studies cited by Novo Nordisk (Pieber *et al* and Rosenstock *et al*), that the data presented by Currie *et al* was *per se* misleading as alleged. The Appeal Board then turned to the materials now at issue in Case AUTH/2141/7/08

The Appeal Board noted that the leavepiece (LAN08/1038) was specifically about the use of Lantus in type 2 diabetics. The final page featured the claim 'In clinical practice, after switching from other treatments, Lantus is associated with a lower risk of hypoglycaemia compared with insulin determir' referenced to pooled data on type 1 and type 2 diabetes from Currie *et al*. Given the specificity of the leavepiece to type 2 diabetes the Appeal Board considered that a claim based on pooled data was misleading. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The Appeal Board noted that use of Currie *et al* and the need to ensure that readers understood that the data was from a mixed group of patients had been at issue in Case AUTH/2038/8/07 where a breach had been ruled. The Appeal Board considered that to again use the data in a way that misled meant that high standards had not been maintained. The Appeal Board upheld the Panel's ruling of a breach of Clause 9.1. The appeal on this point was unsuccessful.

The mailing (LAN08/1041), 'Why choose Lantus' referred to both type 1 and type 2 diabetes patients. As in the leavepiece above the claim at issue had been derived from Currie *et al*. In this instance, however, the Appeal Board considered that as the mailing had referred to both type 1 and type 2 diabetes, the claim based on pooled data from type 1 and 2 patients was not misleading. The Appeal Board ruled no breach of Clause 7.2. The appeal on this point was successful.

Complaint received **14 July 2008**

Case completed **28 October 2008**