CASE AUTH/2038/8/07

NOVO NORDISK v SANOFI-AVENTIS

Promotion of Lantus

Novo Nordisk complained about a Lantus (insulin glargine) mailing sent by Sanofi-Aventis. Novo Nordisk had a competitor product, Levemir (insulin detemir).

Novo Nordisk alleged that a cost comparison claim 'Lantus offers a significant cost advantage over insulin detemir in both type 1 and type 2 diabetes' followed by two bullet points which claimed that Lantus treatment costs were 10% lower and 28% lower (p<0.001) in type 1 and type 2 diabetes respectively, than for insulin detemir, was in breach of the Code. The Poole *et al* reference clearly emphasised that there was a significant difference between the two products in terms of the applied insulin regimens in type 2 diabetes; like had not been compared with like. The more frequent use of basal plus oral regimen with Lantus thus related to lower costs therefore the overall claim about the reduced treatment-related costs in type 2 diabetes was unfair and misleading. Furthermore during the analysed period Levemir did not have a marketing authorization for basal plus oral indication and was used off-label. The Code stated that an economic evaluation must be consistent with the marketing authorization, therefore using Poole *et al* for promotional claims was in breach of the Code.

The Panel noted that the mailing was entitled 'Which basal insulin analogue has lower anti-diabetic prescribing costs compared with Levemir in similar patients?' Beneath 'Once-daily Lantus' it continued 'Evidence from a retrospective database analysis of routine general practice of people with diabetes being initiated on basal insulin therapy'. Page 2 was headed 'Lantus offers a significant cost advantage over Levemir in both type 1 and type 2 diabetes'.

Pages 1 and 2 were referenced to Poole *et al* which compared the costs of diabetes treatments, administration and monitoring following initiation of treatment with glargine or detemir regimens in type 1 or type 2 diabetes mellitus patients, using a database of UK patients treated in general practice. The study showed that prescribing costs were significantly lower in patients treated with glargine than those treated with detemir. The authors noted that the key difference between glargine and detemir was their pharmacokinetic profile and hence their posology – glargine was administered once daily and detemir either once or twice daily. With type 1 diabetics the median cost of prescriptions was 10% lower (p<0.001) amongst those treated with glargine than those treated with detemir. In two of the five components of the overall prescribing cost (sharps and hypoglycaemia rescue medication) the cost difference did not achieve statistical significance. Among type 2 diabetics the median cost of prescriptions was 28.1% lower amongst those treated with glargine compared with detemir (p<0.001). The largest single contribution to this was the difference in insulin cost, 31.7% lower in the glargine group (p<0.001). The median cost per year of oral antidiabetic medicine was slightly higher in the glargine group than the detemir group but this difference did not achieve statistical significance (p=0.096). Irrespective of treatment regimens the volume of insulin prescribed to patients with type 2 diabetes was consistently lower among those treated with glargine than detemir, whether standardized for basal exposure, or for both basal insulin exposure and patient's weight.

The Panel noted the authors' view that the results might have been influenced as detemir was only recommended in patients with type 2 diabetes as part of a basal-bolus regimen although clearly it could be used as a basal-oral anti-diabetic regimen. The authors also noted that further research needed to be undertaken to evaluate the long-term cost effectiveness of glargine over detemir. The Panel was concerned that this important caveat was not reflected in the material at issue. However the Panel did not consider the cost comparison misleading due to the more frequent use of the basal plus insulin regimen as alleged. No breach of the Code was ruled.

The Panel noted that there appeared to be a difference of views regarding the Levemir indication which according to Sanofi-Aventis had not changed. Currie *et al* (2007) which looked at similar data stated that in interpreting the evaluations there might be a familiarity effect with regard to glargine since it was launched earlier (2002 rather than 2004) and that the licence for detemir did not include management of type 2 diabetes except as part of a basal-bolus regimen. The Panel noted that the dates of first authorization in the SPCs were 9 June 2000 for Lantus and 1 June 2004 for Levemir. Poole *et al* stated that when the study was conducted from 2004 it was possible some physicians might have felt more comfortable prescribing glargine which had been available for a longer period than detemir and this might have influenced the results. Levemir could be used with oral anti-diabetics. The Panel queried whether the changes to Section 5.1 of the Levemir SPC would affect the prescription costs. However the Panel did not accept that the mailing was necessarily misleading if during the analysed period Levemir did not have a licence for the basal plus oral indication. At the time the mailing was sent Section 5.1 of the SPC referred to the use of Levemir with oral anti-diabetics. No breach of the Code was ruled.

Novo Nordisk was concerned that the claim 'Lantus significantly reduced hypoglycaemia over Levemir in

both type 1 and type 2 diabetes' highlighted that significant risk reduction was observed separately in type 1 and type 2 diabetes, whilst Currie *et al*'s analysis of hypoglycaemic events was conducted on the pooled patient cohort involving both types of diabetes. Since hypoglycaemic risk was clearly different in type 1 and type 2 diabetes, this claim was misleading. Further, the claim was substantiated with a retrospective cohort analysis, despite there being head-to-head randomized clinical trials both in type 1 and type 2 diabetes with very different results and conclusions. In fact hypoglycaemic risk (major and nocturnal hypoglycaemic events) was significantly lower in the case of Levemir when it was compared with Lantus as part of basal-bolus therapy in type 1 diabetes (Pieber *et al* 2007). In type 2 diabetes these insulin preparations did not differ from a safety perspective when they were compared as part of basal plus oral regimen (Rosenstock *et al* 2006). Novo Nordisk alleged that claim did not reflect all the available evidence and thus it was misleading in breach of the Code.

The Panel noted the heading at page 3 'Lantus significantly reduces hypoglycaemia over Levemir in both type 1 and type 2 diabetes' was referenced to Currie *et al* which examined as a secondary endpoint the relative risk of hypoglycaemia of Levemir and Lantus and changes in weight. Analysis was conducted on a pooled patient cohort of type 1 and type 2 diabetics. The heading did not make this sufficiently clear and was misleading in this regard. A breach of the Code was ruled.

The Panel noted that the first bullet point on page 3 explained that the data was derived from a retrospective database analysis of routine general practice of people with diabetes. The Panel noted that in Pieber *et al* cited by Novo Nordisk, the overall risk of hypoglycaemia was similar with no differences in confirmed hypoglycaemia. The Panel considered that it was sufficiently clear that the data derived from an observational study. Readers would be aware, in general terms of the differences between observational studies and randomized clinical trials. The Panel did not consider on the basis of the two studies cited by Novo Nordisk that the data presented from Currie *et al* was per se misleading as alleged. No breach of the Code was ruled.

Novo Nordisk noted that the claims 'Lantus and insulin detemir had a similar effect on weight in people with type [sic] diabetes' and 'In people with type 2 diabetes, effect on weight was comparable with Lantus and insulin detemir' appeared as bullet points on page 3 of the mailing. Both were referenced to Currie *et al*. The Levemir summary of product characteristics (SPC) stated that it caused significantly less weight gain in type 2 patients than other basal insulin preparations such as Lantus when used as part of basal plus oral regimen (Levemir had been licensed for this indication since March 2007). This claim was based on Rosenstock *et al* (2006). The claims disregarded evidence from a trial providing a higher level of evidence than a retrospective cohort analysis, not to mention the Levemir SPC. Furthermore the authors concluded that, '… detemir showed benefits in terms of weight gain whereby those patients who switched to detemir had on average no evidence of any weight gain in the period following switching treatment', clearly drawing attention to this potential benefit of Levemir. Therefore the claims highlighting the equivalence of the two preparations contradicted the original intention of the authors in breach of the Code. Novo Nordisk alleged that the mailing was unfair, ambiguous, seriously misleading information and disparaged Levemir.

The Panel noted that Section 5.1 of the Levemir SPC stated that studies in patients with type 2 diabetes treated with basal insulin in combination with oral anti-diabetic medicines glycaemic control (HbA1C) with Levemir was comparable to NPH insulin and Lantus and associated with less weight gain. The Panel considered that there was a difference between the products in relation to weight gain in type 2 diabetics. A table illustrated the change in body weight after treatment with insulin. A 52 week study demonstrated a weight gain of 2.3kg and 3.7kg respectively for Levemir once or twice daily – and 4kg gain for Lantus. The statistical significance of this difference was not given. Novo Nordisk stated that the SPC data for weight gain was based on Rosenstock *et al* which compared Levemir and Lantus. The abstract stated that bodyweight increased less with Levemir than with Lantus in completers (3kg vs 3.9kg, p= 0.012) and in the intention to treat analysis (2.7kg vs 3.5kg, p= 0.03).

The Panel considered that the claims regarding effect on weight were misleading as they did not reflect the Levemir SPC regarding weight gain in type 2 diabetics. A breach of the Code was ruled. Upon appeal by Sanofi-Aventis the Appeal Board considered that the claims at issue were misleading as they did not reflect the totality of the data regarding the weight gain typically seen with Lantus and Levemir. The Appeal Board upheld the Panel's ruling of a breach of the Code.

In Pieber *et al* the change in body weight after 26 weeks' treatment in type 1 diabetics was not statistically significantly different with Levemir and Lantus (0.52kg vs 0.96kg, p = 0.193).

The claims at issue were referenced to Currie et at wherein type 2 diabetics treated with detemir appeared to show almost no weight gain on average in the first 6 months of treatment whereas those treated with glargine gained 0.5kg on average. These differences did not achieve statistical significance (p = 0.78). The discussion section noted that Levemir showed benefits in terms of weight gain whereby those patients who switched to Levemir had on average no evidence of any weight gain. The Panel considered, however, that there was an important difference between stating that two products were comparable to stating that there was no statistically significant difference between them. On balance the Panel considered that the claims at issue were inconsistent with the authors' views in Currie *et al* as alleged. A breach of the Code was ruled.

Novo Nordisk Limited complained about a mailing (ref API 07/1039) for Lantus (insulin glargine) sent by Sanofi-Aventis to UK health professionals with an interest in diabetes in May 2007. Novo Nordisk produced a competitor product, Levemir (insulin detemir).

Novo Nordisk stated that it had failed to resolve matters with Sanofi-Aventis, and was reluctant to engage in conciliation as it considered that the mailer had already caused significant damage to the reputation of Levemir. Due to the nature of this one-off mailing Novo Nordisk considered that the only acceptable way to resolve this matter would be a corrective statement from Sanofi-Aventis. Sanofi-Aventis had ignored this request.

1 Claim 'Lantus offers a significant cost advantage over insulin detemir in both type 1 and type 2 diabetes'

This claim on page 2 of the mailing was followed by two bullet points which claimed that Lantus treatment costs were 10% lower and 28% lower ($p<0.001$) in type 1 and type 2 diabetes respectively, than for insulin detemir. All of the claims were referenced to a retrospective data analysis by Poole *et al* (2007).

COMPLAINT

Novo Nordisk alleged that the cost comparison was in breach of Clause 7.2 of the Code since Poole *et al* clearly emphasised that there was a significant difference between the two products in terms of the applied insulin regimens in type 2 diabetes. Poole *et al* thus did not compare like with like. The more frequent use of basal plus oral regimen with Lantus thus related to lower costs therefore the overall claim about the reduced treatment-related costs in type 2 diabetes was unfair and misleading. Furthermore during the analysed period Levemir did not have a licence for basal plus oral indication which meant that this economic evaluation also analyzed data from patients who used Levemir off-label. Whilst it was widely acceptable to report such data as part of an independent peer-reviewed scientific publication, using it for promotional purposes placed this issue at a different angle. The supplementary information to Clause 7.2 of the Code stated that an economic evaluation must be consistent with the marketing authorization, therefore using Poole *et al* for promotional claims was in breach of the Code.

RESPONSE

Sanofi-Aventis stated that the mailing reported on data from two peer-reviewed publications examining the effectiveness and prescribing costs of Lantus compared with Levemir in the treatment of type 2 diabetes. These studies were observational, retrospective, database analyses performed from one of the UK's largest general practice research databases (The Health Improvement Network (THIN) comprising records from over 5 million patients registered with a UK GP).

With regard to the allegation that the comparison on prescribing costs was unfair, inferring that Sanofi-Aventis had failed to comply with the supplementary information to Clause 7.2 that, 'valid comparisons can only be made where like is compared with like', Sanofi-Aventis understood that this requirement related to price comparisons, ie a comparison of the unit cost of individual medicines, not a comparison of the cost of treatment of conditions.

Sanofi-Aventis submitted that in applying the Code correctly, the requirement of such a cost comparison was that 'Care must be taken to ensure that economic evaluation … is borne out by the data available and does not exaggerate its significance'. The mailing undertook a robust assessment of the data available, the studies were performed according to protocols approved by an independent ethics committee and peer reviewed prior to publication. The size of the THIN database and the fact that it represented such a significant proportion of the UK population implied that the findings were appropriate to generalise to the UK as a whole, and were likely to accurately represent the true effectiveness and cost-effectiveness of the products when used in the UK. Therefore the significance of the results was relevant to the audience and was not exaggerated, in keeping with the requirements of the Code for such an economic comparison.

With regard to the concern that the two patient groups were not identical and that this implied that a fair comparison was not possible, Sanofi-Aventis submitted that the information reported simply captured the different use of the products in day-to-day clinical practice. Whilst in a randomised controlled trial (RCT) a demographic imbalance between patient groups would be a significant source of bias, a RCT would fail to detect differences due to unequal utilisation rates in normal practice. The great strength of a real life observational study was that any difference detected reflected the real usage pattern of the products, and this was essential if an accurate cost and cost-effectiveness analysis was to be performed - the economic case would only be valid if it fully took into account how the products were used in practice. This was particularly so in this case, where it might be relevant that the different rates of treatment with additional antidiabetic agents might be due to the differences in the effectiveness of the products. To suggest that such a comparison was unfair and misleading was misguided - by their very nature, effectiveness and cost-effectiveness needed to incorporate such differences at their core to properly understand how products were effective in clinical practice.

Novo Nordisk had suggested that a difference in the individual product licences in force for the period studied might account for different rates of use of concomitant oral antidiabetic agents between the two products, stating that the combination of Levemir and oral hypoglycaemic agents was not specifically indicated (off-label) during this time. However, the current marketing authorization for Levemir showed that the indication 'Treatment of diabetes mellitus',

was the same now as when the study was performed (Levemir summary of product characteristics (SPC) 1 June 2004) and this was comparable to that for Lantus ('For the treatment of adults, adolescents and children of 6 years or above with diabetes mellitus, where treatment with insulin is required'). Both these indications remained generalised to the treatment of diabetes, and neither precluded the concomitant use of oral antidiabetic agents during the period studied. Although the marketing authorization for Levemir had subsequently benefited from the addition to Section 5.1 of information about its use with oral antidiabetic agents, the 2004 SPC certainly did not preclude their concomitant use, which occurred in 27% of patients in this study. There was no such restriction stated in either the contraindications or warnings/precautions sections, and the section on drug interactions suggested that doses of concomitant oral agents might need to be reduced when used with Levemir, implying a common expectation of concomitant use of this class of medicine.

In summary, the evidence supporting the economic argument was appropriate, it being a robust, peer-reviewed analysis of the observed use of the products compared in the setting of everyday practice in the UK health environment and, contrary to the argument of Novo Nordisk, was consistent with not only the current marketing authorizations but also the marketing authorizations relevant to the period in which the data was collected. This complied with the Code and high standards had been maintained.

PANEL RULING

The Panel noted that the mailing was entitled 'Which basal insulin analogue has lower anti-diabetic prescribing costs compared with Levemir in similar patients?' Beneath 'Once-daily Lantus' it continued 'Evidence from a retrospective database analysis of routine general practice of people with diabetes being initiated on basal insulin therapy'. Page 2 was headed 'Lantus offers a significant cost advantage over Levemir in both type 1 and type 2 diabetes'.

Pages 1 and 2 were referenced to Poole *et al* which compared the costs of diabetes treatments, administration and monitoring following initiation of treatment with glargine or detemir regimens in type 1 or type 2 diabetes mellitus patients. The source data was a database of UK patients treated in general practice. The study showed that prescribing costs were significantly lower in patients treated with glargine than those treated with detemir. The study authors noted that the key difference between glargine and detemir was their pharmacokinetic profile and hence their posology – glargine was administered once daily and detemir either once or twice daily. With type 1 diabetics the median cost of prescriptions was 10% lower ($p<0.001$) amongst those treated with glargine than those treated with detemir. In two of the five components of the overall prescribing cost (sharps and hypoglycaemia rescue medication) the cost difference did not achieve statistical significance. Among type 2 diabetics the median cost of prescriptions was 28.1% lower amongst those treated with glargine compared with detemir ($p<0.001$). The largest single contribution to this was the difference in insulin cost, 31.7% lower in the glargine group ($p<0.001$). The median cost per year of oral antidiabetic medicine was slightly higher in the glargine group than the detemir group but this difference did not achieve statistical significance ($p=0.096$). Irrespective of treatment regimens the volume of insulin prescribed to patients with type 2 diabetes was consistently lower among those treated with glargine than detemir, whether standardized for basal exposure, or for both basal insulin exposure and patient's weight.

The Panel noted the authors' view that the results might have been influenced as detemir was only recommended in patients with type 2 diabetes as part of a basal-bolus regimen although clearly it could be used as a basal-oral anti-diabetic regimen. The authors also noted that further research needed to be undertaken to evaluate the long-term cost effectiveness of glargine over detemir. The Panel was concerned that this important caveat was not reflected in the material at issue. However the Panel did not consider the cost comparison misleading due to the more frequent use of the basal plus insulin regimen as alleged. No breach of Clause 7.2 was ruled.

The Panel noted that there appeared to be a difference of views regarding the Levemir indication which according to Sanofi-Aventis had not changed. Currie *et al* (2007) which looked at similar data stated that in interpreting the evaluations there might be a familiarity effect with regard to glargine since it was launched earlier (2002 rather than 2004) and that the licence for detemir did not include management of type 2 diabetes except as part of a basal-bolus regimen. The Panel noted that the dates of first authorization in the SPCs were 9 June 2000 for Lantus and 1 June 2004 for Levemir. Poole *et al* stated that when the study was conducted from 2004 it was possible some physicians might have felt more comfortable prescribing glargine which had been available for a longer period than detemir and this might have influenced the results. Levemir could be used with oral anti-diabetics. The Panel queried whether the changes to Section 5.1 of the Levemir SPC would affect the prescription costs. However the Panel did not accept that the mailing was necessarily misleading if during the analysed period Levemir did not have a licence for the basal plus oral indication. At the time the mailing was sent Section 5.1 of the SPC referred to the use of Levemir with oral anti-diabetics. No breach of Clause 7.2 was ruled on this point.

During its consideration of this matter the Panel considered that, from the claims at issue, prescribers would assume that the prescribing costs for all of their type 1 and all of their type 2 diabetics would be 10% and 28% lower if they prescribed Lantus instead of Levemir respectively. The Panel queried whether this was so based on median costs. The claims at issue did not refer to median costs. The Panel requested that the parties be advised of its concerns in this regard.

2 Claim 'Lantus significantly reduced hypoglycaemia over Levemir in both type 1 and type 2 diabetes'

This claim appeared as a bullet point on page 3 of the mailing referenced to Currie *et al*. This claim was followed by a bullet point which stated that in a retrospective data analysis of routine general practice of diabetics being initiated on basal insulin therapy showed that hypoglycaemia was reduced by 30% when they switched from other treatments to Lantus. The claim was referenced to Currie *et al* which, as with Poole *et al* above, used data from the THIN database.

COMPLAINT

Novo Nordisk had two major concerns.

Firstly the claim highlighted that significant risk reduction was observed separately in type 1 and type 2 diabetes, whilst in Currie *et al*, analysis on hypoglycaemic events was conducted on the pooled patient cohort involving both types of diabetes. Since hypoglycaemic risk was clearly different in type 1 and type 2 diabetes, this claim was misleading. Secondly, the claim was substantiated with a paper publishing a retrospective cohort analysis, despite there being head-to-head randomized clinical trials both in type 1 and type 2 diabetes with very different results and conclusions. In fact hypoglycaemic risk (major and nocturnal hypoglycaemic events) was significantly lower in the case of Levemir when it was compared with Lantus as part of basal-bolus therapy in type 1 diabetes (Pieber *et al* 2007). In type 2 diabetes these insulin preparations did not differ from a safety perspective when they were compared as part of basal plus oral regimen (Rosenstock *et al* 2006). Novo Nordisk alleged that claim did not reflect all the available evidence and thus it was misleading in breach of Clause 7.2 of the Code.

RESPONSE

Sanofi-Aventis submitted that the statement 'both type 1 and type 2' was intended to convey the concept of a pool of patients with both type 1 and type 2 diabetes, as opposed to a single cohort of patients with one of type 1 or type 2 disease.

Whilst Sanofi-Aventis agreed that if taken in isolation this headline might appear ambiguous, when placed in context with the rest of the data on the page the meaning became clear. The detailed text that explained the headline stated that the reductions in hypoglycaemia were observed in 'people with diabetes' - implying a pooling of patients with both types of the disease. Taking the page as a whole into consideration, the information presented was consistent with the published data - to omit to mention that the study contained patients with both type 1 and type 2 diabetes would be inappropriate, and the detailed text made it clear it was a pooled comparison of patients.

Sanofi-Aventis noted that Novo Nordisk had contested that the data observed in real life did not match exactly those seen in RCTs and suggested that this was therefore not a fair summary of all the information available (although only two RCTs were cited in making this argument). Whilst agreeing that RCT data were often fundamental to the evaluation of any new product or intervention, 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. A large observational study such as Currie *et al* was much more generalisable to the population than a small RCT and, contrary to Sanofi-Aventis's suggestion, a good quality observational study was rated level 2b in standard evidence based medicine hierarchies, the same level as a poor quality RCT.

Although individual RCT reporting was generally high quality, overall reporting of product-related trials was generally accepted to be susceptible to bias; Pieber *et al* cited by Novo Nordisk was a good example of this. The choice of evening-only administration of Lantus was questionable (the marketing authorization suggested dosing at any time of day) and had the effect of introducing a trial design that better favoured Levemir. Although Novo Nordisk highlighted the statistically significant differences in hypoglycaemia (higher in the Lantus group) it failed to mention the fact that the overall risk of hypoglycaemia was similar with no differences in confirmed hypoglycaemia. This inappropriate omission of the more significant comparison was in itself disingenuous.

In summary, the claims made from this observational study were a true representation of the effectiveness of the products in normal practice that had been demonstrated by appropriate scientific methodology, and as such significantly added to the evidence base available. The results were not inconsistent with the marketing authorizations and had been reported in a fashion that was consistent with the Code.

PANEL RULING

The Panel noted the heading at page 3 'Lantus significantly reduces hypoglycaemia over Levemir in both type 1 and type 2 diabetes' was referenced to Currie *et al* which examined as a secondary endpoint the relative risk of hypoglycaemia of Levemir and Lantus and changes in weight. Analysis was conducted on a pooled patient cohort of type 1 and type 2 diabetics. The heading did not make this sufficiently clear and was misleading in this regard. A breach of Clause 7.2 was ruled.

The Panel noted that the first bullet point on page 3 explained that the data was derived from a retrospective database analysis of routine general practice of people with diabetes. The Panel noted that in Pieber *et al* cited by Novo Nordisk, the overall risk of hypoglycaemia was similar with no differences in confirmed hypoglycaemia. The Panel considered that it was sufficiently clear that the data derived from an observational study. Readers would be aware, in general terms of the differences between observational studies and randomized clinical trials. The Panel did not consider on the basis of the two studies cited by

Novo Nordisk that the data presented from Currie *et al* was per se misleading as alleged. No breach of Clause 7.2 was ruled.

3 Claims 'Lantus and insulin detemir had a similar effect on weight in people with type [sic] diabetes' and 'In people with type 2 diabetes, effect on weight was comparable with Lantus and insulin detemir'

These claims appeared as bullet points on page 3 of the mailing. Both were referenced to Currie *et al*.

COMPLAINT

Novo Nordisk alleged that the claims at issue were in breach of Clause 7.2 of the Code. The Levemir summary of product characteristics (SPC) stated that it caused significantly less weight gain in type 2 patients than other basal insulin preparations such as Lantus when used as part of basal plus oral regimen (Levemir had been licensed for this indication since March 2007). This claim was based on Rosenstock *et al* (2006). The claims disregarded evidence from a trial providing a higher level of evidence than a retrospective cohort analysis, not to mention the Levemir SPC. Furthermore the authors (Currie *et al*), concluded that, '… detemir showed benefits in terms of weight gain whereby those patients who switched to detemir had on average no evidence of any weight gain in the period following switching treatment', clearly drawing attention to this potential benefit of Levemir. Therefore the claims highlighting the equivalence of the two preparations contradicted the original intention of the authors in breach of Clause 11.4 of the Code.

Novo Nordisk alleged that the mailing was in breach of Clause 7.2 in several aspects. It contained unfair, ambiguous, seriously misleading information and disparaged Levemir.

RESPONSE

Sanofi-Aventis noted that Novo Nordisk had stated that the SPC specifically stated that Levemir caused significantly less weight gain in type 2 patients than other basal insulin preparations. Sanofi-Aventis could find no such statement of significance in the SPC. Although the SPC stated that lower levels of weight gain were seen with Levemir, there was no attribution of significance (which was however specifically mentioned for several other comparisons), and the figures for weight gain in the SPC were different from those cited by Rosenstock *et al* that the Novo Nordisk provided to support its position. The claims in the mailing on weight gain were therefore not inconsistent with the marketing authorizations for either product.

Sanofi-Aventis agreed that Currie *et al* noted that 'patients who switched to Levemir had on average no evidence of weight gain'. The mailing did not contest this point - it simply reported the findings of the study which were that patients treated with Lantus had comparable levels of weight change to those treated with Levemir. (Interestingly, this was also reported by, Pieber *et al* 2007, where levels of weight change were not different between the two products). In total, the claims about weight gain met the requirements of the Code and high standards had been maintained.

In summary, the mailing was a fair representation of a well designed, well reported observational study that was widely generalisable to the UK population. This was not inconsistent with the marketing authorization for either product now (when the study was reported) or in 2004 (the time from which the data in the study was examined). The item complied with the Code and high standards had been maintained.

Finally, Sanofi-Aventis noted that Novo Nordisk had raised the issue that, inter-company discussions Sanofi-Aventis had failed to address the request that a corrective statement be sent to all those who received the original item. Having addressed all the concerns raised in the initial complaint, Sanofi-Aventis submitted its response made this moot. However, as Novo Nordisk had again raised this request, Sanofi-Aventis would of course issue such a statement if this item was ruled to be in breach of the Code to the degree that the Code of Practice Appeal Board considered this was appropriate, but recognised that it was the appropriate body to make this decision not Novo Nordisk.

PANEL RULING

Section 5.1 of the Levemir SPC stated that studies in patients with type 2 diabetes treated with basal insulin in combination with oral anti-diabetic medicines glycaemic control (HbA1C) with Levemir was comparable to NPH insulin and Lantus and associated with less weight gain. The Panel considered that there was a difference between the products in relation to weight gain in type 2 diabetics. A table illustrated the change in body weight after treatment with insulin. A 52 week study demonstrated a weight gain of 2.3kg and 3.7kg respectively for Levemir once or twice daily – and 4kg gain for Lantus. The statistical significance of this difference was not given. Novo Nordisk stated that the SPC data for weight gain was based on Rosenstock *et al* which compared Levemir and Lantus. The abstract stated that bodyweight increased less with Levemir than with Lantus in completers (3kg vs 3.9kg, p= 0.012) and in the intention to treat analysis (2.7kg vs 3.5kg, p= 0.03).

The Panel considered that the claims regarding effect on weight were misleading as they did not reflect the statement in the Levemir SPC regarding weight gain in type 2 diabetics. A breach of Clause 7.2 of the Code was ruled. This ruling was appealed.

In Pieber *et al* the change in body weight after 26 weeks treatment in type 1 diabetics was not statistically significantly different with Levemir and Lantus (0.52kg vs 0.96kg, p = 0.193).

The claims at issue were referenced to Currie et at wherein type 2 diabetics treated with detemir appeared to show almost no weight gain on average in the first 6 months of treatment whereas those treated with glargine gained 0.5kg on average. These

differences did not achieve statistical significance (p = 0.78). The discussion section noted that Levemir showed benefits in terms of weight gain whereby those patients who switched to Levemir had on average no evidence of any weight gain. The Panel considered, however, that there was an important difference between stating that two products were comparable to stating that there was no statistically significant difference between them. On balance the Panel considered that the claims at issue were inconsistent with the authors' views in Currie *et al* as alleged. A breach of Clause 11.4 was ruled. This ruling was not appealed.

APPEAL BY SANOFI-AVENTIS

Sanofi-Aventis noted that the mailing contained the claim that 'Lantus and insulin detemir had a similar effect on weight …' referenced to Currie *et al* that had demonstrated a minimal change in weight (1kg or less over 9 months) with no significant difference between the two products.

Sanofi-Aventis noted that the Panel considered this claim to be misleading as the data were contrary to a statement in the Levemir SPC. Although Sanofi-Aventis acknowledged that the Levemir SPC stated that the product was associated with less weight gain than Lantus, it did not consider that the claim had misrepresented or misled regarding the effect of Levemir on weight. The Levemir SPC indicated that the product caused weight gain to some degree and the promotional claim was consistent with this.

Sanofi-Aventis submitted that the new finding that it had reported was essentially that the weight change associated with Lantus was lower in this study than that previously recognised, and it was not unreasonable to draw attention to this new information concerning Lantus, not Levemir. Although this statement was no longer consistent with the Levemir SPC sentence 'associated with less weight gain', this was not due to a change in or suggestion that the existing knowledge of Levemir was incorrect - at no stage did this paper or the claim suggest that the change in weight associated with Levemir was any different from that recognised in the SPC.

In principle Sanofi-Aventis submitted that it was important to be able to present new data concerning a company's own products, and that it was unreasonable that dissemination of new data was restricted by mention of a product's properties in a competitor's SPC - a competitor company might not be motivated to update out-of-date information. It should also be considered that there might be instances of conflicting information between the SPCs of a product and the mention of the same in the SPC of another medicine. How could a claim be made that would always be contrary to one of the SPCs?

In summary, Sanofi-Aventis submitted that the claim that the level of weight gain seen with Lantus was lower than previously reported, and this was not inconsistent with the Lantus SPC. The claim did not challenge the concept that Levemir was also associated with weight gain, which was also consistent with the Levemir SPC. The only inconsistency with the claim was that the new data presented on Lantus meant that the Levemir SPC now contained out-of-date data on Lantus, and Sanofi-Aventis submitted that to be restricted by this was neither rational nor reasonable from a scientific and medical standpoint.

COMMENTS FROM NOVO NORDISK

Novo Nordisk noted that the claim that Lantus and Levemir had comparable effects on weight in type 2 diabetes was substantiated by Currie *et al* which reported results of a retrospective database analysis of proprietary data from The Health Improvement Network. The authors compared the outcomes of care in people with type 1 and type 2 diabetes following switching to treatment with either Lantus or Levemir in UK routine general practice. One of the secondary outcomes of this analysis was to compare weight changes after switching. The paper did not state anything about weight changes in type 1 diabetes but only showed a graph without making any conclusion. In terms of the findings from type 2 diabetes the paper also presented a graph and reported no weight gain in the first 6 months of treatment with Levemir and a 0.5kg average weight gain with Lantus; the difference was not statistically significant.

Novo Nordisk stated that it was aware that it was not the scope of its comment to criticise Currie *et al*, a scientific paper published by independent authors. Indeed Novo Nordisk had emphasised its concerns regarding the validity of the findings in an appropriate scientific way and sent a letter to the editor of the journal (Freemantle *et al*, 2007). However during the analysed time period there was a major difference between the parts of the SPCs which specified how Levemir and Lantus could be used in the treatment of diabetes mellitus. While Lantus could be used as a part of either basal+oral or basal-bolus regimens, Levemir could only be used as part of basal-bolus therapy, at that time. Although there was no data from this perspective in the paper, one had to assume that a considerably higher proportion of patients used a basal+oral regimen in the Lantus group than in the Levemir group since this regimen was the most popular way to start insulin therapy in type 2 diabetes. Therefore the authors did not compare 'like with like' in the case of type 2 diabetes. Novo Nordisk noted that despite finding a statistically, non-significant weight gain difference between the two products in type 2 diabetes, the authors had highlighted in the Discussion section that '…[Levemir] showed benefits in terms of weight gain whereby those patients who switched to [Levemir] had on average no evidence of any weight gain in the period following switching treatment'.

Novo Nordisk alleged that using only one reference to substantiate a promotional claim and disregarding all the other evidence showing exactly the opposite, as well as neglecting the relevant statement from the Levemir SPC, was cherry-picking the data.

In terms of other evidence Novo Nordisk first noted

the statement from the Levemir SPC that 'Studies in patients with type 2 diabetes treated with basal insulin in combination with oral antidiabetic drugs demonstrates that glycaemic control (HbA1c) with Levemir is comparable with NPH insulin and [Lantus] and associated with less weight gain, please see table 2 below.'

Table 2 set out the change in body weight after treatment with insulin determir, NPH insulin and insulin glargine at 20, 26 and 52 weeks.

Novo Nordisk stated that this was a clear statement, from the highest level of evidence, that Levemir had a weight benefit compared to Lantus in type 2 diabetes when insulin treatment was started. The statement was scientifically based on the results from a head-to-head comparison of the two preparations as part of basal+oral therapy in a randomized clinical trial (Rosenstock *et al*).

Furthermore Novo Nordisk noted that Levemir had been shown to cause less weight gain than Lantus when used as part of basal+bolus therapy in type 2 diabetes (Raskin *et al* 2006). In a randomized controlled clinical trial, a head-to-head comparison of the two compounds revealed a significant difference in terms of treatment-associated weight gain. While patients on Levemir therapy (+rapid-acting insulin analogue at mealtimes) gained an average 1.4kg during the 26 weeks of the trial, treatment with Lantus resulted in an average weight gain of 2.9kg (inter-group difference 1.48kg, p<0.0026).

Novo Nordisk noted that due to the limited amount of data from head-to-head comparisons between Levemir and Lantus, it also highlighted the weight results from randomized clinical trials when the two basal analogues were compared with NPH insulin. Firstly Novo Nordisk noted results from clinical trials where the basal insulin preparations were applied as part of basal+oral therapy.

Novo Nordisk had conducted two clinical trials in which Levemir was compared to NPH insulin in patients who were previously insulin-naïve (Hermansen *et al* 2006). The use of Levemir was associated with an average weight gain of 1.2kg during the 26-week long trial period, whilst NPH insulin caused an average weight gain of 2.8kg (difference 1.6kg, p<0.001). Further analysis of these results showed that the higher the patient's body mass index (BMI) at baseline, the smaller the weight gain he/she experienced.

Novo Nordisk noted that this association was also confirmed by Philis-Tsimikas *et al*, (2007), where the Levemir associated weight gain was 0.7kg whilst the weight gain in the NPH arm was 1.6kg (difference 0.9kg, p=0.005). This weight gain was observed in the trial arms where the insulin preparations were given in the evening, which was the traditional way to use the basal+oral combination (Philis-Tsimikas *et al* 2006)

Novo Nordisk noted that different results were seen in terms of the randomized clinical trials where Lantus was used as part of basal+oral therapy. Lantus was launched five years ago and Sanofi-Aventis had conducted several clinical trials, a summary of the weight results from these trials was provided.

	Weight change with) insulin glargine (kg)	**Weight change NPH insulin (kg)**	**p**
Fritsche *et al*, 2003	+3.7±3.6*	+2.9±4.3*	p=NS
Yki-Jarvinen *et al*, 2006	+2.6±0.6	+3.5±0.7	p=NS
Yki-Jarvinen *et al*, 2000	+2.57±0.23	+2.34±0.23	p=NS
HOE 901/2004 Study Investigators Group 2003	+0.31 (insulin glargine 30) +0.64 (insulin glargine 80)	+0.68	p-value was not published
Riddle *et al*, 2003	+3.0±0.2	+2.8±0.2	p=NS
Rosenstock et al, 2001**	+0.4	+1.4	p<0.0007

* in case of injecting the insulin preparations in the evening

** 62% of the patients on the Lantus arm used bolus insulin preparation as well, whilst in the NPH arm 64% of the subjects applied bolus insulin.

Novo Nordisk noted that it had conducted two randomized controlled trials in type 2 diabetes and focused on basal-bolus therapy, comparing Levemir with NPH insulin as the basal part of the regimen. In Haak *et al*, (2004), use of Levemir was associated with an average weight gain of 1kg whilst the NPH group gained an average of 1.8kg (p=0.017). Raslova *et al*, 2004, revealed an average weight gain of 0.51kg in the Levemir group vs 1.13kg in the NPH group (p=0.038). However in this latter trial the authors compared a full analogue basal-bolus regimen (insulin detemir + insulin aspart) with a full human insulin regimen (NPH insulin + human soluble insulin), therefore the difference in weight gain could not solely be attributed to the difference between the basal preparations. Regarding basal-bolus randomized clinical trials in type 2 diabetes with Lantus, the only one Novo Nordisk could identify was Rosenstock *et al*, (see table above) which studied a mixed group of previously insulin-naïve or insulin-treated patients with type 2 diabetes.

Novo Nordisk submitted that scientific theories, might explain why these basal insulin analogues had different impacts on patients' weight. There were two areas undergoing investigation, both theories explained the observed weight difference by the different mode of action of the two preparations. After injection into the human body the mode of action of Lantus was similar to that of NPH insulin, whilst Levemir acted in a different way. The molecule of Levemir was acylated with a free fatty acid chain through which it bound to albumin molecules in the body.

Novo Nordisk alleged that the first theory explained the weight benefit of Levemir with its relative hepato-selectivity compared to other exogenous insulin

preparations, such as Lantus. In normal physiology there was a portal-peripheral insulin gradient in the human body, since insulin was normally secreted into the portal vein system. In the case of exogenous insulin preparations this hepato-peripheral gradient was shifted towards the peripheral tissues causing relative hyperinsulinaemia in target organs (eg muscle, fat). Since the Lantus albumin complex could not penetrate through the endothelium in the peripheral tissues, but could penetrate the liver because of the fenestrated capillary wall in the sinusoids, the relative peripheral hyperinsulinaemia was shifted back to the portal system, which might decrease the peripheral lipogenesis in patients treated with Levemir. This relative hepato-selectivity was confirmed by a clamp trial involving healthy volunteers and comparing Levemir with NPH insulin (Hordern *et al*, 2005).

Novo Nordisk alleged that the other hypothesis explained the weight benefit with increased insulin signalling in the hypothalamus with Levemir compared to NPH insulin (Hennige *et al*, 2006). Since this part of the central nervous system played a crucial role in the control of satiety, this theory assumed that Levemier might have an enhanced effect on this part of the brain thus it might affect the satiety of patients in a favourable way.

Novo Nordisk alleged that on the basis of the above, the amount and perhaps more importantly the level of medical evidence suggesting a weight benefit of Levemir, when compared with Lantus and NPH insulin, was more than capable of substantiation. The medical evidence was further strengthened by the biological and pharmacological plausibility of the mechanisms underlying this consistent benefit of Levemir.

Therefore Novo Nordisk agreed that the claims at issue were misleading and were in breach Clause 7.2 of the Code. Further, Novo Nordisk also agreed with the Panel's ruling that the claims were inconsistent with the views of Currie *et al* and were in breach of Clause 11.4. In fact Novo Nordisk failed to understand how Sanofi-Aventis had appealed against the Panel's ruling of a breach of Clause 7.2 but not against the breach of Clause 11.4.

APPEAL BOARD RULING

The Appeal Board noted that the claims at issue 'Lantus and insulin detemir had a similar effect on weight in people with type [sic] diabetes' and 'In people with type 2 diabetes, effect on weight was comparable with Lantus and insulin detemir' were referenced to Currie *et al*, an observational study, wherein type 2 diabetics treated with Levemir appeared to show almost no weight gain on average in the first 6 months of treatment whereas those treated with Lantus gained 0.5kg on average. This difference did not achieve statistical significance ($p = 0.78$).

The Appeal Board noted however that a number of randomised clinical trials had shown that Levemir was associated with less weight gain than Lantus.

The Appeal Board considered that the claims at issue were misleading as they did not reflect the totality of the data regarding the weight gain typically seen with Lantus and Levemir. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The appeal was unsuccessful.

Complaint received	**21 August 2007**
Case completed	**4 February 2008**